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Patentanmeldung Nr. Patent application No. Demande de brevet n°

02027120.1

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Imidazole-derivatives as factor xa inhibitors

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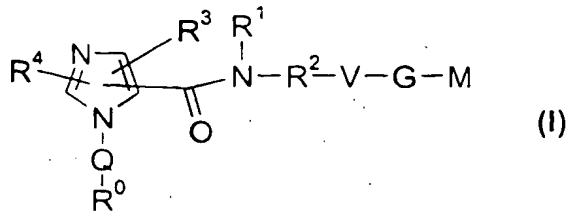
Description

Imidazole-derivatives as factor Xa inhibitors

The present invention relates to compounds of the formula I,



(I)

in which R^0 ; R^1 ; R^2 ; R^3 ; R^4; Q; V, G and M have the meanings indicated below. The compounds of the formula I are valuable pharmacologically active compounds. They exhibit a strong antithrombotic effect and are suitable, for example, for the therapy and prophylaxis of cardiovascular disorders like thromboembolic diseases or restenoses. They are reversible inhibitors of the blood clotting enzymes factor Xa (FXa) and/or factor VIIa (FVIIa), and can in general be applied in conditions in which an undesired activity of factor Xa and/or factor VIIa is present or for the cure or prevention of which an inhibition of factor Xa and/or factor VIIa is intended. The invention furthermore relates to processes for the preparation of compounds of the formula I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical preparations comprising them.

Normal haemeostasis is the result of a complex balance between the processes of clot initiation, formation and clot dissolution. The complex interactions between blood cells, specific plasma proteins and the vascular surface, maintain the fluidity of blood unless injury and blood loss occurs (EP-A-987274). Many significant disease states are related to abnormal haemeostasis. For example, local thrombus formation due to rupture of atheroslerotic plaque is a major cause of acute myocardial infarction and unstable angina. Treatment of an occlusive coronary thrombus by either thrombolytic therapy or percutaneous angioplasty may be accompanied by acute thrombolytic reclosure of the affected vessel.

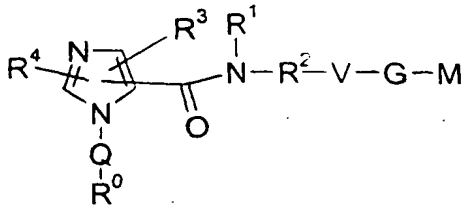
There continues to be a need for safe and effective therapeutic anticoagulants to limit or prevent thrombus formation. It is most desirable to develop agents that inhibit coagulation without directly inhibiting thrombin but by inhibiting other steps in the coagulation cascade like factor Xa and/or factor VIIa activity. It is now believed that inhibitors of factor Xa carry a lower bleeding risk than thrombin inhibitors (A. E. P. Adang & J. B. M. Rewinkel, Drugs of the Future 2000, 25, 369-383).

Low molecular weight, factor Xa-specific blood clotting inhibitors that are effective but do not cause unwanted side effects have been described, for example, in WO-A-95/29189. However, besides being an effective factor Xa-specific blood clotting inhibitor, it is desirable that such inhibitors also have further advantageous properties, for instance stability in plasma and liver and selectivity versus other serine proteases whose inhibition is not intended, such as thrombin. There is an ongoing need for further low molecular weight factor Xa specific blood clotting inhibitors, which are effective and have the above advantages as well.

Specific inhibition of the factor VIIa/tissue factor catalytic complex using monoclonal antibodies (WO-A-92/06711) or a protein such as chloromethyl ketone inactivated factor VIIa (WO-A-96/12800, WO-A-97/47651) is an extremely effective means of controlling thrombus formation caused by acute arterial injury or the thrombotic complications related to bacterial septicemia. There is also experimental evidence suggesting that inhibition of factor VIIa/tissue factor activity inhibits restenosis following balloon angioplasty. Bleeding studies have been conducted in baboons and indicate that inhibition of the factor VIIa/tissue factor complex has the widest safety window with respect to therapeutic effectiveness and bleeding risk of any anticoagulant approach tested including thrombin, platelet and factor Xa inhibition. Certain inhibitors of factor VIIa have already been described. EP-A-987274, for example discloses compounds containing a tripeptide unit, which inhibit factor VIIa. However, the property profile of these compounds is still not ideal, and there is an ongoing need for further low molecular weight factor VIIa inhibitory blood clotting inhibitors

The present invention satisfies the above needs by providing novel compounds of the formula I, which exhibit better factor Xa and/or factor VIIa inhibitory activity and are favorable agents with high bioavailability.

Thus, the present invention relates to compounds of the formula I,



(I)

wherein

R^0 is 1) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8,

2) a monocyclic or bicyclic 4- to 15-membered heteroaryl out of the group pyridyl, pyrimidinyl, indolyl, isoindolyl, indazolyl, phthalazinyl, quinolyl, isoquinolyl, benzothiophen, quinazolinyl and phenylpyridyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, or

3) a monocyclic or bicyclic 4- to 15-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, and which is additionally substituted by a monocyclic or bicyclic 4- to 15-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

R8 is 1) halogen,

2) $-NO_2$,

3) -CN,

4) $-C(O)-NH_2$,

5) -OH,

6) $-NH_2$,

7) $-O-CF_3$

8) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by halogen or $-O-(C_1-C_8)$-alkyl,

9) $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue, or

10) $-O-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,

11) $-SO_2-CH_3$ or

12) $-SO_2-CF_3$,

provided that R8 is at least one halogen, $-C(O)-NH_2$ or $-O-(C_1-C_8)$-alkyl residue, if R^0 is a monocyclic or bicyclic 6- to 14-membered aryl,

Q is a direct bond, $-(C_0-C_2)$-alkylene-$C(O)-NR^{10}$-, $-NR^{10}-C(O)-NR^{10}$-, $-NR^{10}-C(O)$-, $-SO_2$-, $-(C_1-C_6)$-alkylene, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n$-, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n$-,

$-(CH_2)_m-S-(CH_2)_n-$, $-(CH_2)_m-C(O)-(CH_2)_n-$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-CH(OH)-(CH_2)_n-$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n-$, $-(C_2-C_3)$-alkylene-O-(C_0-C_3)-alkylene-, $-(C_2-C_3)$-alkylene-S(O)-, $-(C_2-C_3)$-alkylene-$S(O)_2-$, $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$, $-(C_2-C_3)$-alkylene-$S(O)_2$-NH-$(R^{10})-$, $-(C_2-C_3)$-alkylene-N$(R^{10})-$ or $-(C_0-C_3)$-alkylene-C(O)-O- ,

wherein R^{10} is as defined below, and wherein n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6, wherein the alkylene residues which are formed by $-(CH_2)_m-$ or $-(CH_2)_n-$ are unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, $-NH_2$ or –OH; or –(C_3-C_6)-cycloalkylen, wherein cycloalkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, $-NH_2$ or –OH;

R^1 is a hydrogen atom, $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13; $-(C_1-C_3)$-alkylene-C(O)-NH-R^0, $-(C_1-C_3)$-alkylene-C(O)-O-R15, a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8, wherein R8 is as defined above; a monocyclic or bicyclic 4- to 15-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen; $-(C_1-C_3)$-perfluoroalkylene, $-(C_1-C_3)$-alkylene-S(O)-(C_1-C_4)-alkyl, $-(C_1-C_3)$-alkylene-$S(O)_2-(C_1-C_3)$-alkyl, $-(C_1-C_3)$-alkylene-$S(O)_2$-N$(R^{4'})-R^{5'}$, $-(C_1-C_3)$-alkylene-O-(C_1-C_4)-alkyl, $-(C_0-C_3)$-alkylene-(C_3-C_8)-cycloalkyl, or $-(C_0-C_3)$-alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, whereas R14 is defined below,

$R^{4'}$ and $R^{5'}$ are independent of one another are identical or different and are hydrogen atom or $-(C_1-C_4)$-alkyl,

R^2 is a direct bond or –(C_1-C_4)-alkylene, or

R^1 and R^3 together with the atoms to which they are bonded form a

4- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

R^1-N-R^2-V form a 4- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is halogen, -OH, =O, -(C_1-C_8)-alkyl, -(C_1-C_4)-alkoxy, -NO_2, -C(O)-OH, -CN, -NH_2, -C(O)-O-(C_1-C_4)-alkyl, -(C_1-C_8)-alkylsulfonyl, -SO_2, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-N-[(C_1-C_8)-alkyl]$_2$, -NR^{18}-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH_2, –S-R^{18}, or –NR^{18}-C(O)-NH-[(C_1-C_8)-alkyl]$_2$,

wherein R^{18} is hydrogen atom, -(C_1-C_3)-perfluoroalkyl or –(C_1-C_6)-alkyl,

V is 1) a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

2) a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or

3) a monocyclic or bicyclic 4- to 15-membered heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

G is a direct bond, -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-CH(OH)-$(CH_2)_n$-, -$(CH_2)_m$-, -$(CH_2)_m$-O-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-NR^{10} -$(CH_2)_n$-, -(CH_2)-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-$(CH_2)_n$-, -(CH_2)-S-$(CH_2)_n$-, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-, -$(CH_2)_m$-O-C(O)-NR^{10}-$(CH_2)_n$- or –$(CH_2)_m$-NR^{10}-C(O)-O-$(CH_2)_n$-,

n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

R^{10} is hydrogen atom, -(C_1-C_3)-perfluoroalkyl or –(C_1-C_6)-alkyl,

M is 1) a hydrogen atom,

2) -(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

3) -C(O)-N(R11)-R12,

4) -$(CH_2)_m$-NR^{10},

5) -(C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

6) -(C_4-C_{15})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

7) -(C_3-C_8)-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

8) a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, wherein R14 is defined above,

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,

2) -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

3) -(C_6-C_{14})-aryl-(C_1-C_4)-alkyl-, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13,

4) -(C_6-C_{14})-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

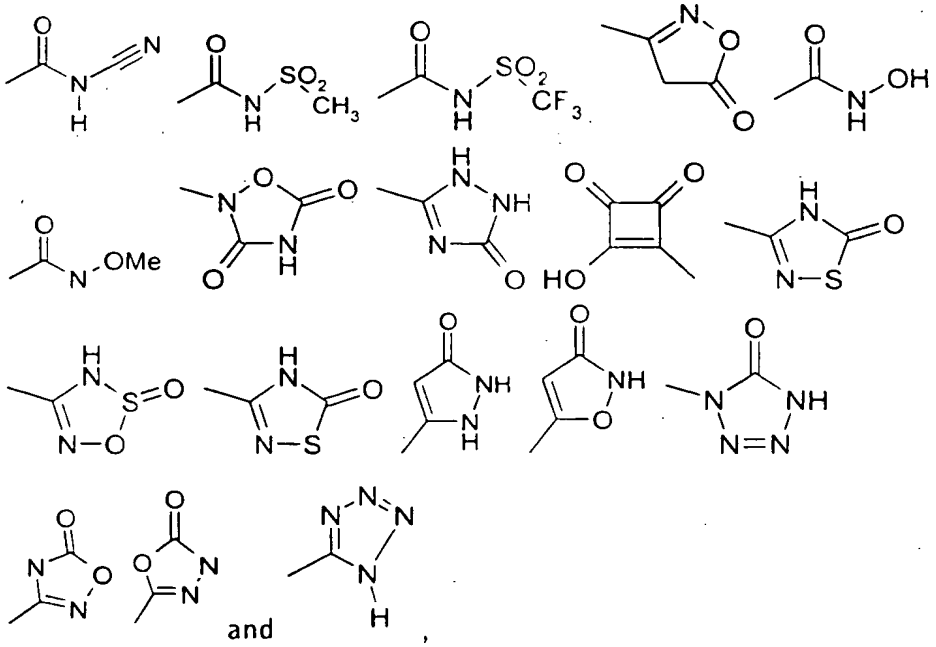
5) -(C_4-C_{15})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13 or

6) -(C_4-C_{15})-heteroaryl-(C_1-C_4)-alkyl-, wherein alkyl and heteroaryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13, or

R11 and R12 together with the nitrogen atom to which they are bonded form a saturated 4- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms

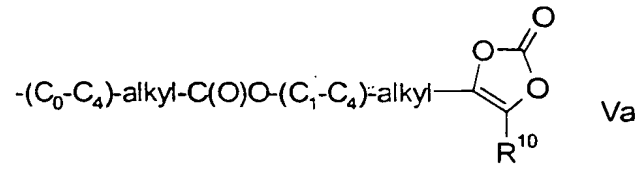
chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

R13 is halogen, $-NO_2$, -CN, =O, -OH, $-(C_1-C_8)$-alkyl, $-(C_1-C_8)$-alkoxy, $-CF_3$, phenyl, phenyloxy-, $-C(O)-O-R^{11}$, phenyl-(C_1-C_4)-alkoxy-, $-C(O)-N(R^{11})-R^{12}$, $-N(R^{11})-R^{12}$, $-NR^{10}-SO_2-R^{10}$, $-S-R^{10}$, $-SO_r-R^{10}$, wherein r is 1 or 2; $-SO_2-N(R^{11})-R^{12}$, $-C(O)-R^{10}$, $-(C_0-C_4)$-alkyl-C(O)-O-C(R15, R16)-O-C(O)-R17, $-(C_0-C_4)$-alkyl-C(O)-O-C(R15, R16)-O-C(O)-O-R17, $-(C_1-C_4)$-perfluoroalkyl, -CN, -O-R15, $-O-CF_3$, -C(O)-O-R15, -C(O)-H, $-NH-C(O)-NH-R^{10}$, -NH-C(O)-O-R15, $-S(O)-(C_1-C_6)$-alkyl, $-S(O)_2-(C_1-C_6)$-alkyl, $-S(O)_2-N(R^{10})-R^{11}$, $-(C_1-C_3)$-alkylene-O-(C_1-C_3)-alkyl, $-NO_2$, or a residue from the following list



and

or a residue of formula Va,



Va

wherein R10, R11 and R12 are as defined above and R15, R16 and R17 are as defined below,

R15 and R16 are independently of one another hydrogen, -(C_1-C_6)-alkyl, or together with the carbon atom to which they are bonded they can form a 3- to 6 membered carbocyclic ring which is unsubstituted or substituted one to three times by R^{10},

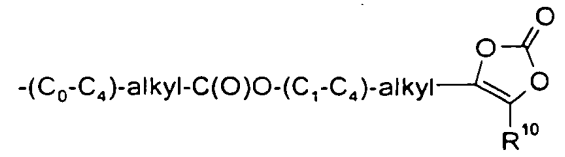
R17 is -(C_1-C_6)-alkyl, -(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-(C_3-C_8)-cycloalkyl wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by R^{10}, and

R^3 and R^4 are independent of one another are identical or different and are

1) hydrogen atom,
2) halogen,
3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13,
4) -(C_1-C_3)-perfluoroalkyl,
5) phenyl, wherein phenyl is unsubstituted or substituted one to three times by R13,
6) -O-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13,
7) -NO_2,
8) -CN,
9) -OH,
10) phenyloxy-, wherein phenyloxy is unsubstituted or substituted one to three times by R13,
11) benzyloxy-, wherein benzyloxy is unsubstituted or substituted one to three times by R13,
12) -C(O)-O-R11,
13) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{12} ,
14) -N(R^{11})-R^{12},
15) -NR^{10}-SO_2-R^{10},
16) -S-R^{10},
17) -SO_s-R^{10}, wherein s is 1 or 2,
18) -SO_2- N(R^{11})-R^{12},
19) -C(O)-R^{10}, wherein R^{10} is as defined above,
20) -C(O)-O-C(R15, R16)-O-C(O)-R17, wherein R15, R16 and R17 are as defined above,

21) -C(O)-O- C(R15, R16)-O-C(O)-O-R17, wherein R15, R16 and R17 are as defined above,

22) a residue of formula Va,



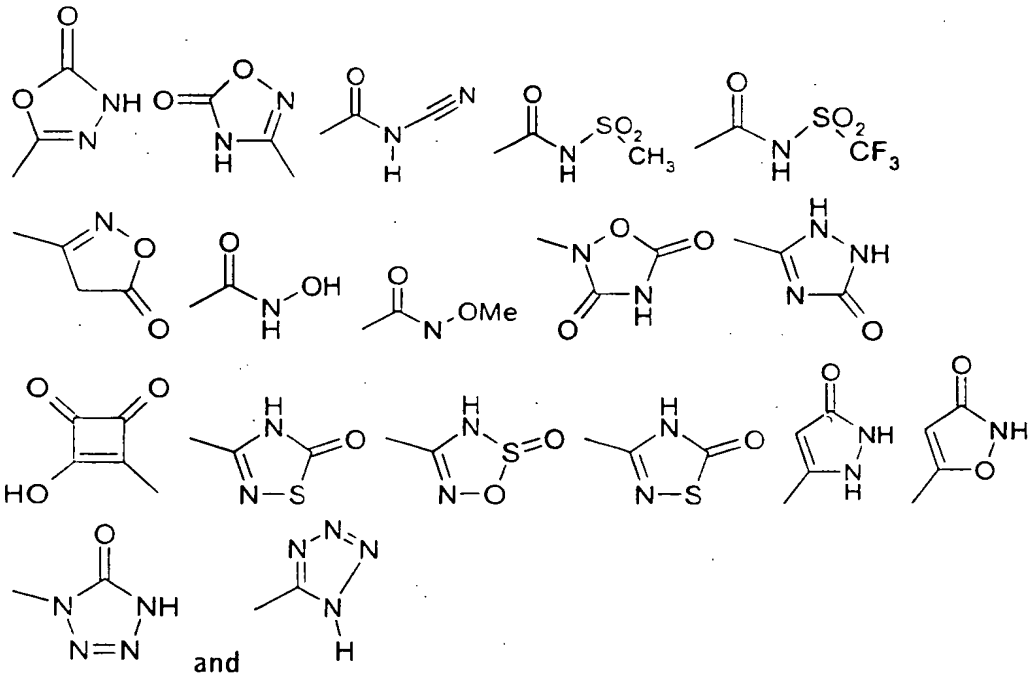
Va

wherein R^{10} is defined as above,

23) $-NR^{10}-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or substituted one, two or three times by R13,

24) $-O-CF_3$,

25) a residue from the following list



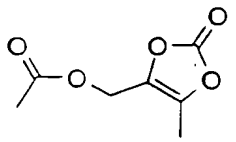
and

26) $-(C_0-C_4)$-alkylene-(C_6-C_{14})-aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R13 and is as defined above,

27) $-(C_0-C_4)$-alkylene-(C_4-C_{15})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

28) $-(C_0-C_2)$alkylene-C(O)-O-(C_1-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

29) $-(C_0-C_2)$alkylene-C(O)-O-(C_1-C_4)-alkylene-O-C(O)-O-(C_1-C_7)-alkyl,



30)

31) -(C_0-C_4)-alkylene-(C_3-C_8)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

32) -(C_0-C_4)-alkylene-het, wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts

The present invention also relates to the compounds of the formula I, wherein

R^0 is 1. a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R^8,

2. a monocyclic or bicyclic 4- to 14-membered heteroaryl out of the group pyridyl, pyrimidinyl, indolyl, isoindolyl, indazolyl, phthalazinyl, quinolyl, isoquinolyl, benzothiophen, quinazolinyl and phenylpyridyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8, or

3. a monocyclic or bicyclic 4- to 14-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8, and which is additionally substituted by a monocyclic or bicyclic 4- to 14-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8,

R^8 is 1. halogen,

2. -NO_2,

3. -CN,

4. -C(O)-NH_2,

5. -OH,

6. -NH_2,

7. –OCF_3

8. a monocyclic or bicyclic 4- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by halogen or –O-(C_1-C_8)-alkyl,

9. -(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue, or

10. –O-(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,

11. $-SO_2CH_3$ or

12. $-SO_2CF_3$,

provided that R^8 is at least one halogen, -C(O)-NH_2 or –O-(C_1-C_8)-alkyl residue, if R^0 is a monocyclic or bicyclic 6- to 14-membered aryl,

Q is a direct bond, -(C_0 –C_2)-alkylen-C(O)-NR^{10}-, -NR^{10}-C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, -(C_1-C_6)-alkylene,

R^1 is a hydrogen atom, -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R^{13}; -(C_1-C_3)-alkylene-C(O)-NH-R^0, -(C_1-C_3)-alkylene-C(O)-O-R^{15}, -(C_1-C_3)-perfluoroalkylene, -(C_1-C_3)-alkylene-S(O)-(C_1-C_4)-alkyl, -(C_1-C_3)-alkylene-$S(O)_2$-(C_1-C_3)-alkyl, -(C_1-C_3)-alkylene-$S(O)_2$-N($R^{4'}$)-$R^{5'}$, -(C_1-C_3)-alkylene-O-(C_1-C_4)-alkyl, -(C_0-C3)-alkylene-(C_3-C_8)-cycloalkyl, or -(C_0-C_3)-alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, whereas R^{14} is defined below,

$R^{4'}$ and $R^{5'}$ are independent of one another are identical or different and are hydrogen atom or -(C_1-C_4)-alkyl,

R^2 is a covalent bond or –(C_1-C_4)-alkylene, or

R^1 and R^3 together with the atoms to which they are bonded can form a 4- to 7-membered cyclic group, containing up to 1 or 2 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

R^1-N-R^2-V can form a 4- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

R^{14} is halogen, -OH, =O, -(C_1-C_8)-alkyl, -(C_1-C_4)-alkoxy, -C(O)-OH, -CN, $-NH_2$, -C(O)-O-(C_1-C_4)-alkyl, -(C_1-C_8)-alkylsulfonyl, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-N-[(C_1-C_8)-alkyl]$_2$, $-NR^{10}$-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH_2, $-NR^{10}$-C(O)-NH-[(C_1-C_8)-alkyl]$_2$, wherein R^{10} is hydrogen atom, -(C_1-C_3)-perfluoroalkyl or –(C_1-C_6)-alkyl,

V is

1. a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
2. a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
3. a monocyclic or bicyclic 4- to 14-membered heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

G is a covalent bond, -$(CH_2)_m$-, -$(CH_2)_m$-O-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-NR^{10}-$(CH_2)_n$-, -(CH_2)-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-, -$(CH_2)_m$-O-C(O)-NR^{10}-$(CH_2)_n$- or –$(CH_2)_m$-NR^{10}-C(O)-O-$(CH_2)_n$-,

n and m are are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

R^{10} is hydrogen atom, -(C_1-C_3)-perfluoroalkyl or –(C_1-C_6)-alkyl,

M is

1. a hydrogen atom,
2. -(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
3. -C(O)-$NR^{11}R^{12}$,
4. -$(CH_2)_m$-NR^{10},
5. -(C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

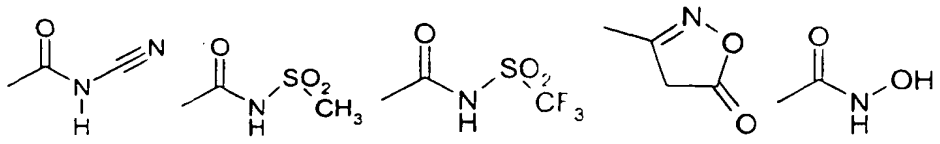
6. -(C_4-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
7. (C_3-C_7)-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
8. a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, wherein R^{14} is defined above,

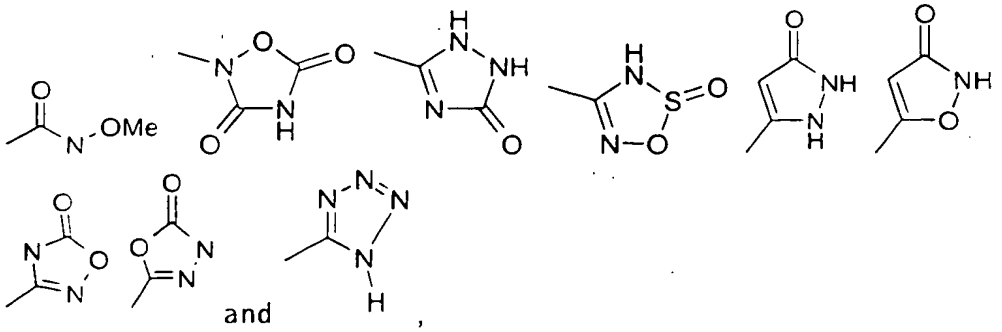
R^{11} and R^{12} are independently of one another identical or different and are

1. hydrogen atom,
2. -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
3. -(C_6-C_{14})-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, or
4. -(C_4-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, or

R^{11} and R^{12} together with the nitrogen atom to which they are bonded can form a saturated 4- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

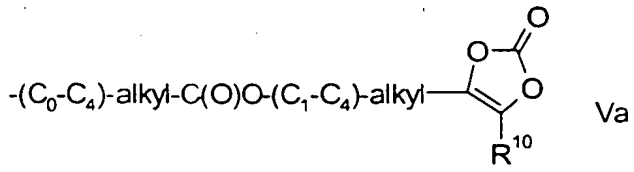
R^{13} is halogen, -NO_2, -CN, =O, -OH, -(C_1-C_8)-alkyl, -(C_1-C_8)-alkoxy, -CF_3, phenyl, phenyloxy-, -C(O)-O-R^{11}, phenyl-(C_1-C_4)-alkoxy-, -C(O)-N-$R^{11}R^{12}$, -$NR^{11}R^{12}$, -NR^{10}-SO_2-R^{10}, -S-R^{10}, -SO_n-R^{10}, wherein n is 1 or 2, -SO_2-$NR^{11}R^{12}$, or -C(O)-R^{10}, -(C_0-C_4)-alkyl-C(O)-O-C($R^{15}R^{16}$)-O-C(O)-R^{17}, -(C_0-C_4)-alkyl-C(O)-O-C($R^{15}R^{16}$)-O-C(O)-O-R^{17}, -(C_1-C_4)-perfluoroalkyl,-CN, -O-R^{15}, -O-CF_3, -C(O)-O-R^{15}, -C(O)-H, -NH-C(O)-NH-R^{10}, -NH-C(O)-O-R^{15}, -S(O)-(C_1-C_6)-alkyl, -$S(O)_2$-(C_1-C_6)-alkyl, -$S(O)_2$- N(R^{10})-R^{11}, -(C_1-C_3)-alkylene-O-(C_1-C_3)-alkyl, or a residue from the following list





and

or a residue of formula Va,



Va

wherein R^{10}, R^{11},R^{12} are as defined above and R^{15}, R^{16} or R^{17} are as defined below,

R^{15} and R^{16} are independently of one another hydrogen, -(C_1-C_6)-alkyl, or together with the carbon atom to which they are bonded they can form a 3- to 6 membered carbocyclic ring which is unsubstituted or substituted one to three times by R^{10},

R^{17} is -(C_1-C_6)-alkyl, -(C_1-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-(C_1-C_8)-cycloalkyl wherein said cycloalkyl ring is unsubstituted or substituted one to three times by R^{10}, and

R^3 and R^4 are independent of one another are identical or different and are

1) hydrogen atom,
2) halogen,
3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R^{13},
4) -(C_1-C_3)-perfluoroalkyl,
5) phenyl, wherein phenyl is unsubstituted or substituted one to three times by R^{13},
6) -O-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R^{13},
7) -CN,
8) -OH,
9) phenyloxy-, wherein phenyloxy is unsubstituted or substituted one to three times by R^{13},
10) benzyloxy-, wherein benzyloxy is unsubstituted or substituted one to three times by R^{13},

11) -C(O)-O-R^{11},

12) -(C_0-C_4)alkyl-C(O)-N-$R^{11}R^{12}$,

13) -$NR^{11}R^{12}$,

14) -NR^{10}-SO_2-R^{10},

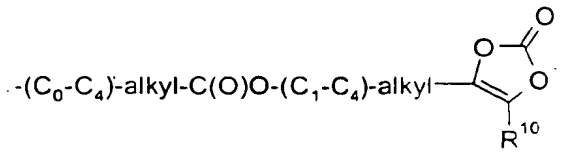
15) -SO_n-R^{10}, wherein n is 1 or 2,

16) -SO_2-$NR^{11}R^{12}$,

17) -C(O)-O-C($R^{15}R^{16}$)-O-C(O)-R^{17}, wherein R^{15}, R^{16} and R^{17} are as defined above,

18) -C(O)-O-C($R^{15}R^{16}$)-O-C(O)O-R^{17}, wherein R^{15}, R^{16} and R^{17} are as defined above,

19) residue of formula Va,



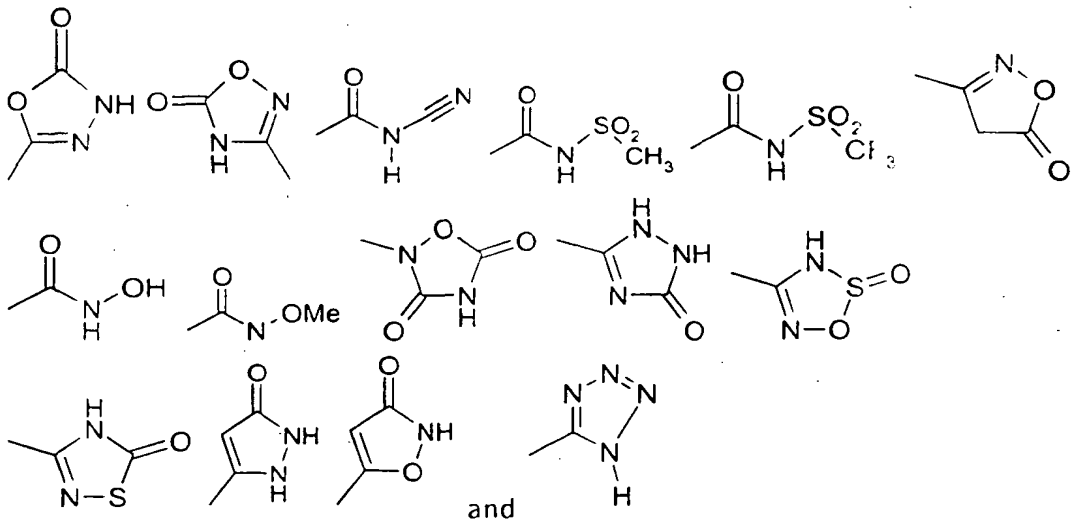
Va

wherein R^{10} is defined as above,

20) -NR^{10}-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R^{13},

21) $-OCF_3$,

22) a residue from the following list



and

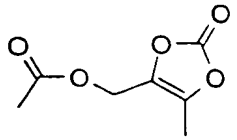
23) -(C_0-C_2)-alkylene-aryl, wherein aryl is a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R^{13}, wherein R^{13} is as defined above,

24) -(C_0-C_2)-alkylene-heteroaryl, wherein heteroaryl is a monocyclic or bicyclic 4- to 15-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen,

wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

25) $-(C_0\text{-}C_2)$alkyl-C(O)-O-$(C_1\text{-}C_4)$-alkyl-O-C(O)-$(C_1\text{-}C_4)$-alkyl,

26) $-(C_0\text{-}C_2)$alkyl-C(O)-O-$(C_1\text{-}C_4)$-alkyl-O-C(O)O-$(C_1\text{-}C_7)$-alkyl,

27)  ,

28) -$(C_0\text{-}C_2)$-alkylene-$(C_3\text{-}C_8)$-cycloalkyl, -$(C_0\text{-}C_3)$-alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

29) -$(C_0\text{-}C_2)$-alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{15}, R^{16} and R^{17} are as defined above,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

3. The present invention also relates to the compounds of the formula I, wherein

R^0 is

1. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8,

2. a bicyclic 5- to 14-membered heteroaryl selected out of the group indolyl, isoindolyl, benzofuranyl, benzothiophenyl, 1,3-benzodioxolyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, chromanyl, isochromanyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, purinyl and pteridinyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8,

and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, , triazolyl, isothiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, pyridazinyl and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8

3. a monocyclic 5- to 14-membered heteroaryl out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8,
and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8

R^8 is 1. halogen, such as F, Cl, Br or J,

2. $-C(O)-NH_2$,

3. $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -OH or a methoxy residue, or

4. $-O-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen or a methoxy residue,

provided that R^8 is at least one halogen, $-C(O)-NH_2$ or $-O-(C_1-C_8)$-alkyl residue, if R^0 is a monocyclic or bicyclic 6- to 14-membered aryl,

Q is a direct bond, -C(O)-; $-SO_2-$ or $-(C_1-C_6)$-alkylen, $-(C_0-C_2)$-alkylen-$C(O)-NR^{10}$-,

R^1 is hydrogen atom or $-(C_1-C_2)$-alkyl, $-(C_1-C_3)$-alkylene-$C(O)-NH-R^0$, $-(C_1-C_3)$-alkylene-$C(O)-O-R^{15}$, $-(C_1-C_3)$-perfluoroalkylene, $-(C_1-C_3)$-alkylene-$S(O)_2-(C_1-C_3)$-alkyl or $-(C_1-C_3)$-alkylene-$S(O)_2-N(R^4)-R^5$,

R^2 is a direct bond or $-(C_1-C_2)$-alkylen, or

R^1-N-R^2-V can form a 4- to 7- membered cyclic group out of the group azetidine, azetidinone, piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

R^{14} is halogen, -OH, =O, -(C_1-C_8)-alkyl, -C(O)-OH, -CN, -NH_2, -C(O)-O-(C_1-C_4)-alkyl, -(C_1-C_8)-alkylsulfonyl, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-N-[(C_1-C_8)-alkyl]$_2$, -C(O)-NH_2, $-NR^{10}$ wherein R^{10} is hydrogen atom, -(C_1-C_3)-perfluoroalkyl or $-(C_1$-$C_6)$-alkyl,

V is 1. a 3- to 7-membered cyclic residue out of the group containing compounds which are derived from aziridine, azirine, azetidine, azetidinone, pyrrole, pyrrolidine, pyridonyl, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, tetrazine, tetrazole, azepine, diazirine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, pyridazine, piperidine, piperazine, pyrrolidinone, ketopiperazine, furan, pyran, dioxole, oxazole, isoxazole, 2-isoxazoline, isoxazolidine, morpholine, oxirane, oxaziridine, 1,3-dioxolene, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxaziridine, thiophene, thiopyran, thietan, thiazole, isothiazole, isothiazoline, isothiazolidine, 1,2-oxathiolan, thiopyran, 1,2-thiazine, 1,3-thiazole, 1,3-thiazine, 1,4-thiazine, thiadiazine or thiomorpholine,

wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

2. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or

3. a bicyclic 5- to 14-membered heteroaryl out of the group quinolyl, isoquinolyl and quinoxalinyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

G is a direct bond, -(CH_2)$_m$-, or -(CH_2)$_m$-NR^{10}-,

m is the integers zero, 1, 2, 3 or 4,

R^{10} is hydrogen atom, -(C_1-C_3)-perfluoroalkyl or -(C_1-C_4)-alkyl,

M is 1. a hydrogen atom,

2. -(C_6-C_{14})-heteroaryl, wherein heteroaryl is a residue out of the group which can be derived from piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, pyridonyl, imidazole, pyridazine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, tetrahydropyran, thiadiazole or thiomorpholine,

wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

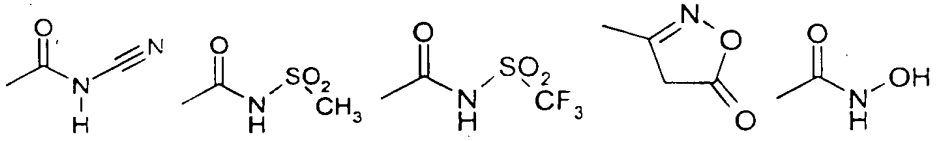
3. -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or

4. (C_3-C_6)-cycloalkyl.

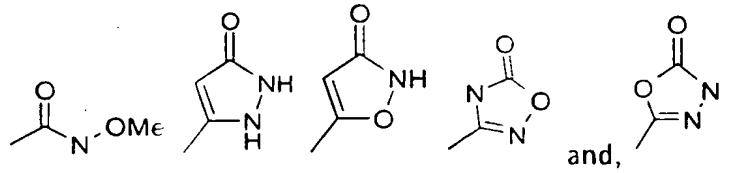
R^{11} and R^{12} together with the nitrogen atom to which they are bonded can form a saturated 4- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

R^{13} is halogen, -NO_2, -CN, =O, -OH, -(C_1-C_8)-alkyl, -(C_1-C_8)-alkoxy, -CF_3, -C(O)-O-R^{11}, -C(O)-N-$R^{11}R^{12}$, -$NR^{11}R^{12}$, -NR^{10}-SO_2-R^{10}, -SO_n-R^{10}, wherein n is 1 or 2; -SO_2-$NR^{11}R^{12}$, -C(O)-R^{10}, -(C_0-C_4)-alkyl-C(O)-O-C($R^{15}R^{16}$)-O-C(O)-R^{17}, -(C_0-C_4)-alkyl-C(O)-O-C($R^{15}R^{16}$)-O-C(O)O-R^{17}, -(C_1-C_4)-perfluoroalkyl,-CN, -O-R^{15}, -O-CF_3, -C(O)-O-R^{15}, -NH-C(O)-NH-R^{10}, -S(O)-(C_1-C_6)-alkyl, -$S(O)_2$-(C_1-C_6)-alkyl, -$S(O)_2$-$N(R^{10})$-R^{11}, -(C_1-C_3)-alkylene-O-(C_1-C_3)-alkyl, or

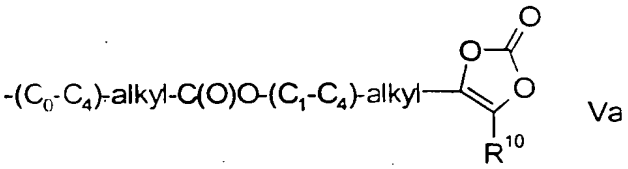
a residue from the following list



and,



or a residue of formula Va,



Va

wherein R^{10}, R^{11},R^{12} are as defined above and R^{15}, R^{16} or R^{17} are as defined below,

R^3 and R^4, are independent of one another are identical or different and are

1) hydrogen atom,

2) halogen,

3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R^{13},

4) -(C_1-C_3)-perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or substituted one to three times by R^{13},

6) -O-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R^{13},

7) -CN,

8) -OH,

9) phenyloxy-, wherein phenyloxy is unsubstituted or substituted one to three times by R^{13},

10) benzyloxy-, wherein benzyloxy is unsubstituted or substituted one to three times by R^{13},

11) -C(O)-O-R^{11},

12) -(C_0-C_4)alkyl-C(O)-N-$R^{11}R^{12}$,

13) -$NR^{11}R^{12}$,

14) -NR^{10}-SO_2-R^{10},

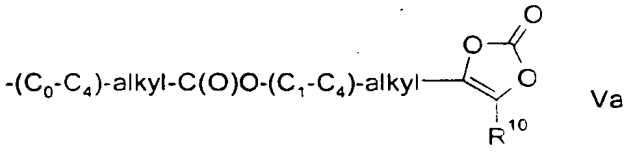
15) -SO_n-R^{10}, wherein n is 1 or 2,

16) -SO_2-$NR^{11}R^{12}$,

17) -C(O)-O-C($R^{15}R^{16}$)-O-C(O)-R^{17}, wherein R^{15}, R^{16} and R^{17} are as defined above,

18) -C(O)-O-C($R^{15}R^{16}$)-O-C(O)O-R^{17}, wherein R^{15}, R^{16} and R^{17} are as defined above,

19) residue of formula Va,



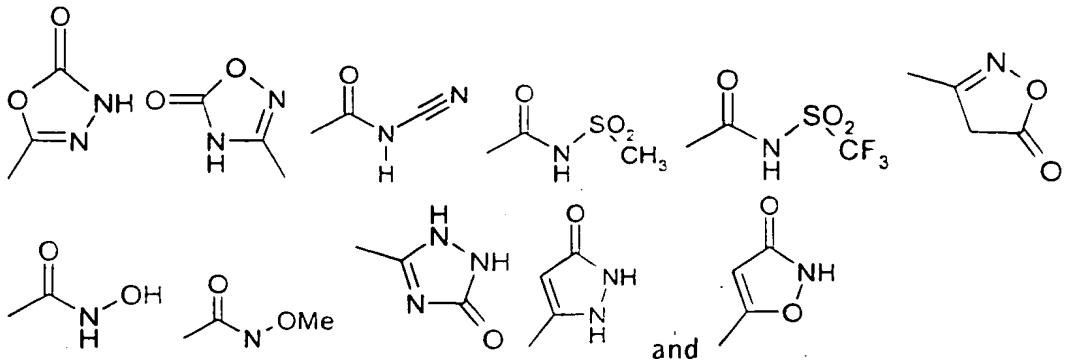
Va

wherein R^{10} is defined as above,

20) -NR^{10}-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R^{13},

21) –OCF_3, or

22) a residue from the following list

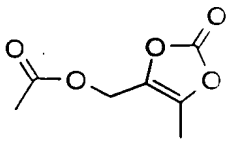


and

23) –(C_0-C_2)alkyl-C(O)-O-(C_1-C_4)-alkyl-O-C(O)-(C_1-C_4)-alkyl,

24) –(C_0-C_2)-alkylene-C(O)-O-(C_1-C_4)-alkylene-O-C(O)-O-(C_1-C_7)-alkyl or

25)



wherein R^{10}, R^{11},R^{12},R^{15}, R^{16} or R^{17} are as defined above,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

4. The present invention also relates to the compounds of the formula I, wherein

R^0 is 1. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8,

2. a bicyclic 5- to 14-membered heteroaryl selected out of the group indolyl, isoindolyl, benzofuranyl, benzothiophenyl, 1,3-benzodioxolyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, chromanyl, isochromanyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, purinyl and pteridinyl,

wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8,

and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, , triazolyl, isothiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, pyridazinyl and

pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8

3. a monocyclic 5- to 14-membered heteroaryl out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8,

and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8

R^8 is 1. halogen, such as F, Cl, Br or J,

2. $-C(O)-NH_2$,

3. $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -OH or a methoxy residue, or

4. $-O-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen or a methoxy residue,

provided that R^8 is at least one halogen, $-C(O)-NH_2$ or $-O-(C_1-C_8)$-alkyl residue, if R^0 is a monocyclic or bicyclic 6- to 14-membered aryl,

Q is a direct bond, -C(O)-; $-SO_2-$ or $-(C_1-C_6)$-alkylen, $-(C_0-C_2)$-alkylen-$C(O)-NR^{10}$-,

R^1 is hydrogen atom or $-(C_1-C_2)$-alkyl,

R^2 is a direct bond or $-(C_1-C_2)$-alkylen, or

R^1-N-R^2-V can form a 5- to 7- membered cyclic group out of the group piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

R^{14} is halogen, $-(C_1-C_4)$-alkyl or $-NH_2$,

R^{11} and R^{12} together with the nitrogen atom to which they are bonded can form a saturated 4- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is

unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

V is 1. a 3- to 7-membered cyclic residue out of the group containing compounds, which are derived from aziridine, azirine, azetidine, pyrrole, pyrrolidine, pyridonyl, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, tetrazine, tetrazole, azepine, diazirine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, pyridazine, piperidine, piperazine, pyrrolidinone, ketopiperazine, furan, pyran, dioxole, oxazole, isoxazole, 2-isoxazoline, isoxazolidine, morpholine, oxirane, oxaziridine, 1,3-dioxolene, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxaziridine, thiophene, thiopyran, thietan, thiazole, isothiazole, isothiazoline, isothiazolidine, 1,2-oxathiolan, thiopyran, 1,2-thiazine, 1,3-thiazole, 1,3-thiazine, 1,4-thiazine, thiadiazine or thiomorpholine,

wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

2. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or

3. a bicyclic 5- to 14-membered heteroaryl out of the group quinolyl, isoquinolyl and quinoxalinyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

G is a direct bond, $-(CH_2)_m-$, or $-(CH_2)_m-NR^{10}-$,

m is the integers zero, 1, 2, 3 or 4,

R^{10} is hydrogen atom, $-(C_1-C_3)$-perfluoroalkyl or $-(C_1-C_4)$-alkyl,

M is 1. a hydrogen atom,

2. $-(C_6-C_{14})$-heteroaryl, wherein heteroaryl is a residue out of the group which can be derived from piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, pyridonyl, imidazole, pyridazine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, tetrahydropyran, thiadiazole or thiomorpholine, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

3. $-(C_1-C_6)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or

4. (C_3-C_6)-cycloalkyl,

$R^3$and R^4 are independent of one another are identical or different and are

1) hydrogen atom,

2) halogen,

3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R^{13},

4) -(C_1-C_3)-perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or substituted one to three times by R^{13},

6) -O-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R^{13},

7) -CN,

8) -OH,

9) -C(O)-O-R^{11},

10) -(C_0-C_4)alkyl-C(O)-N-$R^{11}R^{12}$,

11) -$NR^{11}R^{12}$,

12) -NR^{10}-SO_2-R^{10},

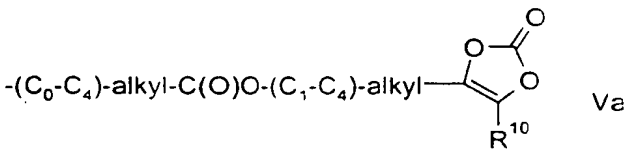
13) -SO_n-R^{10}, wherein n is 1 or 2,

14) -SO_2-$NR^{11}R^{12}$,

15) -C(O)-O-C($R^{15}R^{16}$)-O-C(O)-R^{17}, wherein R^{15}, R^{16} and R^{17} are as defined above,

16) -C(O)-O-C($R^{15}R^{16}$)-O-C(O)O-R^{17}, wherein R^{15}, R^{16} and R^{17} are as defined above,

17) residue of formula Va,



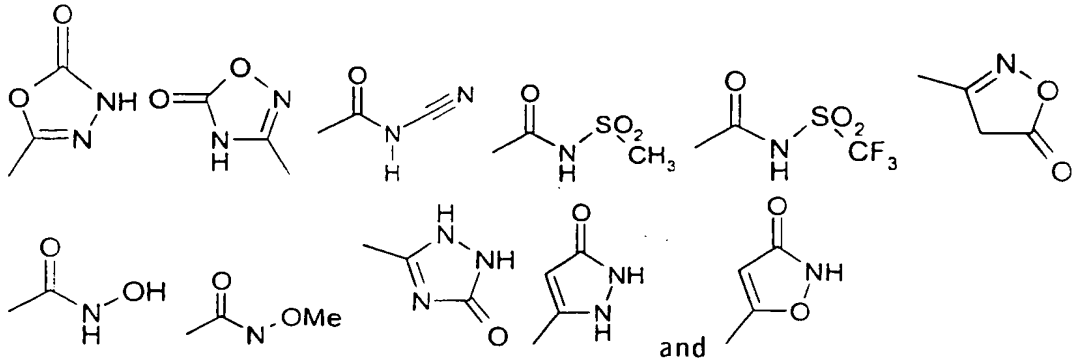
Va

wherein R^{10} is defined as above,

18) -NR^{10}-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R^{13},

19) –OCF_3, or

20) a residue from the following list



molecule. Examples of substituted alkyl residues are alkyl residues in which one or more, for example 1, 2 or 3, hydrogen atoms are replaced with halogen atoms, in particular fluorine atoms.

The term "mono- or bicyclic 4- to 15-membered heteroaryl" or "-(C_4-C_{15})-heteroaryl" refers to (C_4-C_{15})-aryl in which one or more of the 4 to 15 ring carbon atoms are replaced by heteroatoms such as nitrogen, oxygen or sulfur. Examples are azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydrochinolinyl, 2H, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuran, fuaranyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purynyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pryidooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisochinolinyl, tetrahydrochinolinyl, 6H-1,2,5-thiadazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thienyl and xanthenyl. Preferred are pyridyl; such as 2-pyridyl, 3-pyridyl or 4-pyridyl; pyrrolyl; such as 2-pyrrolyl and 3-pyrrolyl; furyl; such as 2-furyl and 3-furyl; thienyl; such as 2-thienyl and 3-thienyl; imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, tetrazolyl, pyridazinyl, pyrazinyl, pyrimidinyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, 1,3-benzodioxolyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, chromanyl, isochromanyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, purinyl and pteridinyl.

The term " R^1-N-R^2-V can form a 4- to 7-membered cyclic group " refers to structures of heterocycles which can be derived from compounds such as piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine.

or an arylalkyl residue. Examples of „-(C_1-C_8)-alkyl" or „-(C_1-C_8)-alkylene" are alkyl residues containing 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms are methyl, methylene, ethyl, ethylene. propyl, propylene, butyl, butylene, pentyl, pentylene, hexyl, heptyl or octyl, the n-isomers of all these residues, isopropyl, isobutyl, 1-methylbutyl, isopentyl, neopentyl, 2,2-dimethylbutyl, 2-methylpentyl, 3-methylpentyl, isohexyl, sec-butyl, tBu, tert-pentyl, sec-butyl, tert-butyl or tert-pentyl. The term „-(C_0-C_6)-alkyl" or „-(C_0-C_8)-alkylene" is a hydrocarbon residues containing 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms. The term „-C_0-alkyl" or „-C_0-alkylene" is a covalent bond.

Unsaturated alkyl residues are, for example, alkenyl residues such as vinyl, 1-propenyl, 2-propenyl (= allyl), 2-butenyl, 3-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 5-hexenyl or 1,3-pentadienyl, or alkynyl residues such as ethynyl, 1-propynyl, 2-propynyl (= propargyl) or 2-butynyl. Alkyl residues can also be unsaturated when they are substituted.

Examples of -(C_3-C_8)-cycloalkyl residues are cycloalkyl residues containing 3, 4, 5, 6, 7 or 8 ring carbon atoms like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyloheptyl or cyclooctyl, which can also be substituted and/or unsaturated. Unsaturated cyclic alkyl groups and unsaturated cycloalkyl groups like, for example, cyclopentenyl or cyclohexenyl can be bonded via any carbon atom.

Of course, a cyclic alkyl group has to contain at least three carbon atoms, and an unsaturated alkyl group has to contain at least two carbon atoms. Thus, a group like (C_1-C_8)-alkyl is to be understood as comprising, among others, saturated acyclic (C_1-C_8)-alkyl, (C_3-C_6)-cycloalkyl, and unsaturated (C_2-C_8)-alkyl like (C_2-C_8)-alkenyl or (C_2-C_8)-alkynyl. Similarly, a group like (C_1-C_4)-alkyl is to be understood as comprising, among others, saturated acyclic (C_1-C_4)-alkyl, and unsaturated (C_2-C_4)-alkyl like (C_2-C_4)-alkenyl or (C_2-C_4)-alkynyl.

Unless stated otherwise, the term alkyl preferably comprises acyclic saturated hydro-carbon residues which have from one to six carbon atoms and which can be linear or branched. A particular group of saturated acyclic alkyl residues is formed by (C_1-C_4)-alkyl residues like methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tBu.

Unless stated otherwise, and irrespective of any specific substituents bonded to alkyl groups which are indicated in the definition of the compounds of the formula I, alkyl groups can in general be unsubstituted or substituted by one or more, for example one, two or three, identical or different substituents. Any kind of substituents present in substituted alkyl residues can be present in any desired position provided that the substitution does not lead to an unstable

2-Bromo-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-1H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

2-(4-Chloro-phenyl)-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

3-[(4-Chloro-phenylcarbamoyl)-methyl]-2-methoxymethyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

1-[(4-Chloro-phenylcarbamoyl)-methyl]-2-methoxymethyl-1H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-ethanesulfonyl-1H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

5-Chloro-3-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]-2-phenyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-cyclopropyl-1H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(2-methoxy-phenyl)-5-methyl-3H- imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(3-trifluoromethyl-phenyl)-3H- imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

In general, the meaning of any group, residue, heteroatom, number etc., which can occur more than once in the compounds of the formula I, is independent of the meaning of this group, residue, heteroatom, number etc. in any other occurrence. All groups, residues, heteroatoms, numbers etc., which can occur more than once in the compounds of the formula I can be identical or different.

As used herein, the term alkyl is to be understood in the broadest sense to mean hydrocarbon residues which can be linear, i. e. straight-chain, or branched and which can be acyclic or cyclic residues or comprise any combination of acyclic and cyclic subunits. Further, the term alkyl as used herein expressly includes saturated groups as well as unsaturated groups which latter groups contain one or more, for example one, two or three, double bonds and/or triple bonds, provided that the double bonds are not located within a cyclic alkyl group in such a manner that an aromatic system results. All these statements also apply if an alkyl group occurs as a substituent on another residue, for example in an alkyloxy residue, an alkyloxycarbonyl residue

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-3H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-1H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-cyclopropyl-3H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(2,6-difluoro-phenyl)-3H-imidazole- 4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-cyclopentyl-3H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(2-methoxy-ethyl)-3H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(2,6-dichloro-phenyl)-3H-imidazole- 4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-isopropyl-3H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-pyridin-2-yl-3H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-2-phenyl-3H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-2-phenyl-1H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-pyridin-3-yl-3H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(2-methyl-thiazol-4-yl)-3H- imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(2-methyl-thiazol-4-yl)-1H- imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

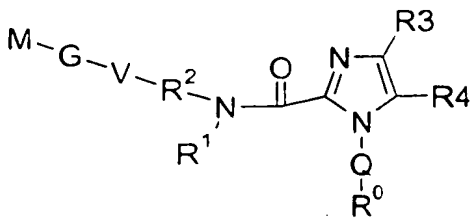
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-ethanesulfonyl-3H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-3H-imidazole-2,4- dicarboxylic acid 2-amide 4-[(1-isopropyl-piperidin-4-yl)-amide]

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-1H-imidazole-2,4- dicarboxylic acid 2-amide 4-[(1-isopropyl-piperidin-4-yl)-amide]

2-Bromo-3-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-3H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

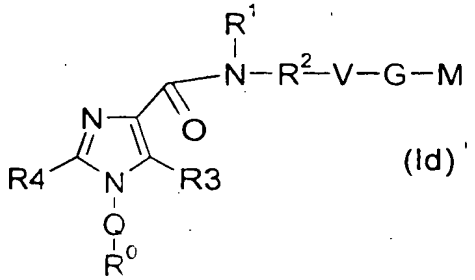
The present invention also relates to the compounds of the formula Ic,



(Ic)

wherein R^0 ; R^1 ; R^2 ; R3 ; R4; Q; V, G and M have the meanings indicated in formula I.

The present invention also relates to the compounds of the formula Id,



(Id)

wherein R^0 ; R^1 ; R^2 ; R3 ; R4; Q; V, G and M have the meanings indicated in formula I.

The present invention also relates to the compounds of the formula I, which are

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-imidazole-4-carboxylic acid (1- isopropyl-piperidin-4-yl)-amide

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-imidazole-4-carboxylic acid (1- isopropyl-piperidin-4-yl)-amide

5-Chloro-3-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-phenyl-3H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

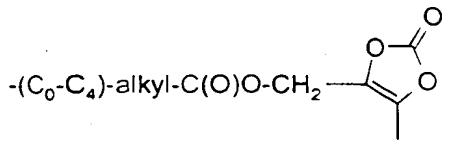
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-ethyl-5-methyl-3H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-ethyl-5-methyl-1H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-iodo-5-methyl-3H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

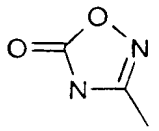
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-iodo-5-methyl-1H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

n) a residue of formula Va

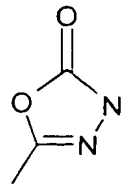


Va

o) a residue of formula Vb or Vc,

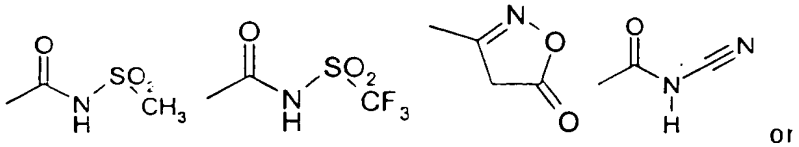


Vb



Vc

p) a residue from the following list



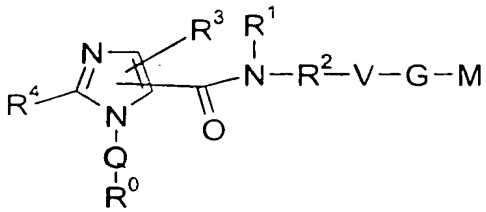
or

q) –CN

r) CF_3

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

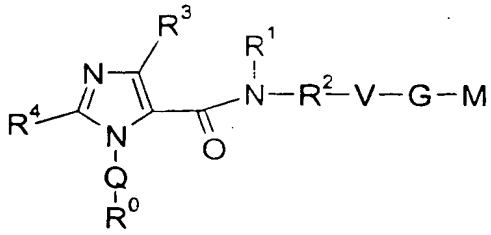
The present invention also relates to the compounds of the formula Ia,



(Ia)

wherein R^0 ; R^1 ; R^2 ; R^3 ; R^4; Q; V, G and M have the meanings indicated in formula I.

The present invention also relates to the compounds of the formula Ib,



(Ib)

wherein R^0 ; R^1 ; R^2 ; R^3 ; R^4; Q; V, G and M have the meanings indicated in formula I.

R^{14} is halogen, methyl, ethyl or $-NH_2$,

V is 1. a residue out of the group containing compounds which is derived from isoquinoline, quinoline, quinazoline, piperidine, azetidine, pyrrolidine, tetrahydropyrane, piperazine and isoxazole, wherein said cyclic residue is unsubstituted or mono- or disubstituted independently of one another by R^{14}, or

2. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R^{14}, or

G is a direct bond, $-(CH_2)_m-$, or $-(CH_2)_m-NR^{10}-$,

m is the integers zero, 1 or 2,

R^{10} is hydrogen atom or $-(C_1-C_4)$-alkyl,

M is a hydrogen atom, (C_2-C_4)-alkyl, imidazolyl, pyrazolyl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, pyridinyl, pyrimidyl, pyrazinyl, pyridazinyl; or (C_3-C_6)-cycloalkyl, wherein said cyclic residues are unsubstituted or mono- or disubstituted independently of one another by R^{14}

R^{11} and R^{12} together with the nitrogen atom to which they are bonded can form a saturated 4- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen out of the group azetidine, pyrrolidine, morpholine, thiomorpholine, piperazine, piperidine; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

R^3 and R^4 are independent of one another are identical or different and are

a) hydrogen atom,

b) F, Cl,

c) $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or substituted by R^{13},

d) phenyl, wherein phenyl is unsubstituted or substituted one to three times by R^{13},

e) $-O-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or substituted by R^{13},

f) $-C(O)-O-R^{11}$,

g) $-(C_0-C_2)$-alkyl-$C(O)-N-R^{11}R^{12}$,

h) $-NR^{11}R^{12}$,

i) $-NR^{10}-SO_2-R^{10}$,

j) $-SO_2-NR^{11}R^{12}$,

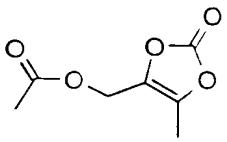
k) $-C(O)-R^{10}$

l) $-C(O)-O-C(R^{15}R^{16})-O-C(O)-R^{17}$, wherein R^{15}, R^{16} and R^{17} are as defined above,

m) $-C(O)-O-C(R^{15}R^{16})-O-C(O)O-R^{17}$, wherein R^{15}, R^{16} and R^{17} are as defined above,

21) —(C_0-C_2)alkyl-C(O)-O-(C_1-C_4)-alkyl-O-C(O)-(C_1-C_4)-alkyl,

22) —(C_0-C_2)alkyl-C(O)-O-(C_1-C_4)-alkyl-O-C(O)O-(C_1-C_7)-alkyl, or

23)  ,

,wherein R^{10}, R^{11},R^{12},R^{15}, R^{16} or R^{17} are as defined above,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

5) The present invention also relates to the compounds of the formula I, wherein

R^0 is 1. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R^8, or

2. a monocyclic 4- to 14-membered heteroaryl out of the group thienyl, thiadiazolyl, isoxazolyl and thiazolyl, wherein said heteroaryl is substituted by a residue selected out of the group thienyl, 2-thienyl and 3-thienyl, wherein said residue is unsubstituted or mono- or disubstituted independently of one another by R^8,

R^8 is F, Cl, Br, $-OCH_3$, $-C(O)-NH_2$ or $-O-CF_3$,

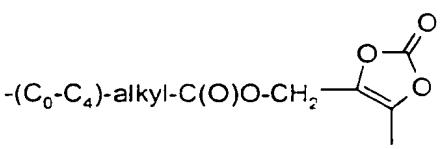
Q is a direct bond, -C(O)-; $-SO_2-$, methylene or ethylene,

R^1 is hydrogen atom,

R^2 is a direct bond or methylen, or

R^1-N-R^2-V can form a 4- to 7-membered cyclic group out of the group azetidine, pyrrolidine, piperidine and piperazine,

R^{13} is -OH, =O, -F, $-CF_3$, $-C(O)-O-R^{11}$, $-C(O)-N-R^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{10}-SO_2-R^{10}$, $-SO_n-R^{10}$, wherein n is 1, 2 or 3; (C_1-C_6)alkyl, (C_0-C_3)alkyl-O-(C_0-C_4)alkyl $-SO_2-NR^{11}R^{12}$, $-C(O)-R^{10}$, $-(C_0-C_4)$-alkyl-C(O)-O-$C(R^{15}R^{16})$-O-C(O)-R^{17}, $-(C_0-C_4)$-alkyl-C(O)-O-$C(R^{15}R^{16})$-O-C(O)O-R^{17}, or a residue of formula Va,



Va

wherein R^{10}, R^{11},R^{12},R^{15}, R^{16} or R^{17} are as defined above,

The term "R15 and R16 are together with the carbon atom to which they are bonded they form a 3- to 6 membered carbocyclic ring" refers to (C_3-C_6)-cycloalkyl structures such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

The term "a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms" refers to structures of heterocycles which can be derived from compounds such as aziridine, azirine, azetidine, pyrrole, pyrrolidine, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, tetrazine, tetrazole, azepine, diazirine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, pyridazine, piperidine, piperazine, pyrrolidinone, ketopiperazine,furan, pyran, dioxole, oxazole, isoxazole, 2-isoxazoline, isoxazolidine, morpholine, oxirane, oxaziridine, 1,3-dioxolene, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxaziridine, thiophene, thiopyran, thietan, thiazole, isothiazole, isothiazoline, isothiazolidine, 1,2-oxathiolan, thiopyran, 1,2-thiazine, 1,3-thiazole, 1,3-thiazine, 1,4-thiazine, thiadiazine or thiomorpholine.

The term"het" refers to structures of heterocycles which can be derived from compounds such as aziridine, azirine, azetidine, pyrrole, pyrrolidine, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, tetrazine, tetrazole, azepine, diazirine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, pyridazine, piperidine, piperazine, pyrrolidinone, ketopiperazine, furan, pyran, dioxole, oxazole, isoxazole, 2-isoxazoline, isoxazolidine, morpholine, oxirane, oxaziridine, 1,3-dioxolene, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxaziridine, thiophene, thiopyran, thietan, thiazole, isothiazole, isothiazoline, isothiazolidine, 1,2-oxathiolan, thiopyran, 1,2-thiazine, 1,3-thiazole, 1,3-thiazine, 1,4-thiazine, thiadiazine or thiomorpholine.

The term "R11 and R12 together with the nitrogen atom to which they are bonded can form a saturated or unsaturated 4- to 7-membered monocyclic heterocyclic ring" refers to residues which can be derived from compounds such as azetidine, azetidinone, piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine.

The fact that many of the before-listed names of heterocycles are the chemical names of unsaturated or aromatic ring systems does not imply that the, the 4-15 membered mono- or polycyclic group could only be derived from the respective unsaturated ring system. The names here only serve to describe the ring system with respect to ring size and the number of the heteroatoms and their relative positions. As explained above, the 4-15 membered mono- or

polycyclic group can be saturated or partially unsaturated or aromatic, and can thus be derived not only from the before-listed heterocycles themselves but also from all their partially or completely hydrogenated analogues and also from their more highly unsaturated analogues if applicable. As examples of completely or partially hydrogenated analogues of the before-listed heterocycles from which this group may be derived the following may be mentioned: pyrroline, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, dihydropyridine, tetrahydropyridine, piperidine, 1,3-dioxolane, 2-imidazoline, imidazolidine, 4,5-dihydro-1,3-oxazol, 1,3-oxazolidine, 4,5-dihydro-1,3-thiazole, 1,3-thiazolidine, perhydro-1,4-dioxane, piperazine, perhydro-1,4-oxazine (= morpholine), perhydro-1,4-thiazine (= thiomorpholine), perhydroazepine, indoline, isoindoline, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, etc.

The 4-15 membered mono- or polycyclic group may be bonded via any ring carbon atom, and in the case of nitrogen heterocycles via any suitable ring nitrogen atom. Thus, for example, a pyrrolyl residue can be 1-pyrrolyl, 2-pyrrolyl or 3-pyrrolyl, a pyrrolidinyl residue can be pyrrolidin-1-yl (= pyrrolidino), pyrrolidin-2-yl or pyrrolidin-3-yl, a pyridinyl residue can be pyridin-2-yl, pyridin-3-yl or pyridin-4-yl, a piperidinyl residue can be piperidin-1-yl (= piperidino), piperidin-2-yl, piperidin-3-yl or piperidin-4-yl. Furyl can be 2-furyl or 3-furyl, thienyl can be 2-thienyl or 3-thienyl, imidazolyl can be imidazol-1-yl, imidazol-2-yl, imidazol-4-yl or imidazol-5-yl, 1,3-oxazolyl can be 1,3-oxazol-2-yl, 1,3-oxazol-4-yl or 1,3-oxazol-5-yl, 1,3-thiazolyl can be 1,3-thiazol-2-yl, 1,3-thiazol-4-yl or 1,3-thiazol-5-yl, pyrimidinyl can be pyrimidin-2-yl, pyrimidin-4-yl (= 6-pyrimidinyl) or 5-pyrimidinyl, piperazinyl can be piperazin-1-yl (= piperazin-4-yl = piperazino) or piperazin-2-yl. Indolyl can be indol-1-yl, indol-2-yl, indol-3-yl, indol-4-yl, indol-5-yl, indol-6-yl or indol-7-yl. Similarly benzimidazolyl, benzoxazolyl and benzothiazol residues can be bonded via the 2-position and via any of the positions 4, 5, 6, and 7. Quinolinyl can be quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl, quinolin-6-yl, quinolin-7-yl or quinolin-8-yl, isoqinolinyl can be isoquinol-1-yl, isoquinolin-3-yl, isoquinolin-4-yl, isoquinolin-5-yl, isoquinolin-6-yl, isoquinolin-7-yl or isoquinolin-8-yl. In addition to being bonded via any of the positions indicated for quinolinyl and isoquinolinyl, 1,2,3,4-tetrahydroquinolinyl and 1,2,3,4-tetrahydroisoquinolinyl can also be bonded via the nitrogen atoms in 1-position and 2-position, respectively.

Unless stated otherwise, and irrespective of any specific substituents bonded to the 4-15 membered mono- or polycyclic group or any other heterocyclic groups which are indicated in the definition of the compounds of the formula I, the 4-15 membered mono- or polycyclic group can be unsubstituted or substituted on ring carbon atoms with one or more, for example one, two, three, four or five, identical or different substituents like (C_1-C_8)-alkyl, in particular (C_1-C_4)-alkyl, (C_1-C_8)-alkyloxy, in particular (C_1-C_4)-alkyloxy, (C_1-C_4)-alkylthio, halogen, nitro, amino,

((C_1-C_4)-alkyl)carbonylamino like acetylamino, trifluoromethyl, trifluoromethoxy, hydroxy, oxo, hydroxy-(C_1-C_4)-alkyl such as, for example, hydroxymethyl or 1-hydroxyethyl or 2-hydroxyethyl, methylenedioxy, ethylenedioxy, formyl, acetyl, cyano, aminosulfonyl, methylsulfonyl, hydroxycarbonyl, aminocarbonyl, (C_1-C_4)-alkyloxycarbonyl, optionally substituted phenyl, optionally substituted phenoxy, benzyl optionally substituted in the phenyl group, benzyloxy optionally substituted in the phenyl group, etc. The substituents can be present in any desired position provided that a stable molecule results. Of course an oxo group cannot be present in an aromatic ring. Each suitable ring nitrogen atom in the 4-15 membered mono- or polycyclic group can independently of each other be unsubstituted, i. e. carry a hydrogen atom, or can be substituted, i. e. carry a substituent like (C_1-C_8)-alkyl, for example (C_1-C_4)-alkyl such as methyl or ethyl, optionally substituted phenyl, phenyl-(C_1-C_4)-alkyl, for example benzyl, optionally substituted in the phenyl group, hydroxy-(C_2-C_4)-alkyl such as, for example 2-hydroxyethyl, acetyl or another acyl group, methylsulfonyl or another sulfonyl group, aminocarbonyl, (C_1-C_4)-alkyloxycarbonyl, etc. In general, in the compounds of the formula I nitrogen heterocycles can also be present as N-oxides or as quaternary salts. Ring sulfur atoms can be oxidized to the sulfoxide or to the sulfone. Thus, for example a tetrahydrothienyl residue may be present as S,S-dioxotetrahydro-thienyl residue or a thiomorpholinyl residue like thiomorpholin-4-yl may be present as 1-oxo-thiomorpholin-4-yl or 1,1-dioxo-thiomorpholin-4-yl. A substituted 4 to 15 membered mono- or polycyclic group that can be present in a specific position of the compounds of formula I can independently of other groups be substituted by substituents selected from any desired subgroup of the substituents listed before and/or in the definition of that group.

The 3-7 membered monocyclic group may be bonded via any ring carbon atom, and in the case of nitrogen heterocycles via any suitable ring nitrogen atom. Thus, for example, a pyrrolyl residue can be 1-pyrrolyl, 2-pyrrolyl or 3-pyrrolyl, a pyrrolidinyl residue can be pyrrolidin-1-yl (= pyrrolidino), pyrrolidin-2-yl or pyrrolidin-3-yl, a pyridinyl residue can be pyridin-2-yl, pyridin-3-yl or pyridin-4-yl, a piperidinyl residue can be piperidin-1-yl (= piperidino), piperidin-2-yl, piperidin-3-yl or piperidin-4-yl. Furyl can be 2-furyl or 3-furyl, thienyl can be 2-thienyl or 3-thienyl, imidazolyl can be imidazol-1-yl, imidazol-2-yl, imidazol-4-yl or imidazol-5-yl, 1,3-oxazolyl can be 1,3-oxazol-2-yl, 1,3-oxazol-4-yl or 1,3-oxazol-5-yl, 1,3-thiazolyl can be 1,3-thiazol-2-yl, 1,3-thiazol-4-yl or 1,3-thiazol-5-yl, pyrimidinyl can be pyrimidin-2-yl, pyrimidin-4-yl (= 6-pyrimidinyl) or 5-pyrimidinyl, piperazinyl can be piperazin-1-yl (= piperazin-4-yl = piperazino) or piperazin-2-yl. Unless stated otherwise, and irrespective of any specific substituents bonded to the 3-7 membered monocyclic group or any other heterocyclic groups which are indicated in the definition of the compounds of the formula I, can be unsubstituted or substituted on ring

carbon atoms with one or more, for example one, two, three, four or five, identical or different substituents like (C_1-C_8)-alkyl, in particular (C_1-C_4)-alkyl, (C_1-C_8)-alkyloxy, in particular (C_1-C_4)-alkyloxy, (C_1-C_4)-alkylthio, halogen, nitro, amino, ((C_1-C_4)-alkyl)carbonylamino like acetylamino, trifluoromethyl, trifluoromethoxy, hydroxy, oxo, hydroxy-(C_1-C_4)-alkyl such as, for example, hydroxymethyl or 1-hydroxyethyl or 2-hydroxyethyl, methylenedioxy, ethylenedioxy, formyl, acetyl, cyano, aminosulfonyl, methylsulfonyl, hydroxycarbonyl, aminocarbonyl, (C_1-C_4)-alkyloxycarbonyl, optionally substituted phenyl, optionally substituted phenoxy, benzyl optionally substituted in the phenyl group, benzyloxy optionally substituted in the phenyl group, etc. The substituents can be present in any desired position provided that a stable molecule results. Of course an oxo group cannot be present in an aromatic ring. Each suitable ring nitrogen atom in the 3-7 membered monocyclic group can independently of each other be unsubstituted, i. e. carry a hydrogen atom, or can be substituted, i. e. carry a substituent like (C_1-C_8)-alkyl, for example (C_1-C_4)-alkyl such as methyl or ethyl, optionally substituted phenyl, phenyl-(C_1-C_4)-alkyl, for example benzyl, optionally substituted in the phenyl group, hydroxy-(C_2-C_4)-alkyl such as, for example 2-hydroxyethyl, acetyl or another acyl group, methylsulfonyl or another sulfonyl group, aminocarbonyl, (C_1-C_4)-alkyloxycarbonyl, etc. In general, in the compounds of the formula I nitrogen heterocycles can also be present as N-oxides or as quaternary salts. Ring sulfur atoms can be oxidized to the sulfoxide or to the sulfone. Thus, for example a tetrahydrothienyl residue may be present as S,S-dioxotetrahydrothienyl residue or a thiomorpholinyl residue like thiomorpholin-4-yl may be present as 1-oxo-thiomorpholin-4-yl or 1,1-dioxo-thiomorpholin-4-yl. A substituted 3-7 membered monocyclic group that can be present in a specific position of the compounds of formula I can independently of other groups be substituted by substituents selected from any desired subgroup of the substituents listed before and/or in the definition of that group.

Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine, particularly preferably chlorine or bromine.

Optically active carbon atoms present in the compounds of the formula I can independently of each other have R configuration or S configuration. The compounds of the formula I can be present in the form of pure enantiomers or pure diastereomers or in the form of mixtures of enantiomers and/or diastereomers, for example in the form of racemates. The present invention relates to pure enantiomers and mixtures of enantiomers as well as to pure diastereomers and mixtures of diastereomers. The invention comprises mixtures of two or of more than two stereoisomers of the formula I, and it comprises all ratios of the stereoisomers in the mixtures. In case the compounds of the formula I can be present as E isomers or Z isomers (or cis isomers

or trans isomers) the invention relates both to pure E isomers and pure Z isomers and to E/Z mixtures in all ratios. The invention also comprises all tautomeric forms of the compounds of the formula I.

Diastereomers, including E/Z isomers, can be separated into the individual isomers, for example, by chromatography. Racemates can be separated into the two enantiomers by customary methods, for example by chromatography on chiral phases or by resolution, for example by crystallization of diastereomeric salts obtained with optically active acids or bases. Stereochemically uniform compounds of the formula I can also be obtained by employing stereochemically uniform starting materials or by using stereoselective reactions.

Physiologically tolerable salts of the compounds of formula I are nontoxic salts that are physiologically acceptable, in particular pharmaceutically utilizable salts. Such salts of compounds of the formula I containing acidic groups, for example a carboxyl group COOH, are for example alkali metal salts or alkaline earth metal salts such as sodium salts, potassium salts, magnesium salts and calcium salts, and also salts with physiologically tolerable quaternary ammonium ions such as tetramethylammonium or tetraethylammonium, and acid addition salts with ammonia and physiologically tolerable organic amines, such as methylamine, dimethylamine, trimethylamine, ethylamine, triethylamine, ethanolamine or tris-(2-hydroxyethyl)amine. Basic groups contained in the compounds of the formula I, for example amino groups or guanidino groups, form acid addition salts, for example with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid or phosphoric acid, or with organic carboxylic acids and sulfonic acids such as formic acid, acetic acid, oxalic acid, citric acid, lactic acid, malic acid, succinic acid, malonic acid, benzoic acid, maleic acid, fumaric acid, tartaric acid, methanesulfonic acid or p-toluenesulfonic acid. Compounds of the formula I, which simultaneously contain a basic group and an acidic group, for example a guanidino group and a carboxyl group, can also be present as zwitterions (betaines) which are likewise included in the present invention.

Salts of compounds of the formula I can be obtained by customary methods known to those skilled in the art, for example by combining a compound of the formula I with an inorganic or organic acid or base in a solvent or dispersant, or from other salts by cation exchange or anion exchange. The present invention also includes all salts of the compounds of the formula I which, because of low physiologically tolerability, are not directly suitable for use in pharmaceuticals but are suitable, for example, as intermediates for carrying out further chemical modifications of

the compounds of the formula I or as starting materials for the preparation of physiologically tolerable salts.

The present invention furthermore includes all solvates of compounds of the formula I, for example hydrates or adducts with alcohols.

The invention also includes derivatives and modifications of the compounds of the formula I, for example prodrugs, protected forms and other physiologically tolerable derivatives, as well as active metabolites of the compounds of the formula I. The invention relates in particular to prodrugs and protected forms of the compounds of the formula I, which can be converted into compounds of the formula I under physiological conditions. Suitable prodrugs for the compounds of the formula I, i. e. chemically modified derivatives of the compounds of the formula I having properties which are improved in a desired manner, for example with respect to solubility, bioavailability or duration of action, are known to those skilled in the art. More detailed information relating to prodrugs is found in standard literature like, for example, Design of Prodrugs, H. Bundgaard (ed.), Elsevier, 1985; Fleisher et al., Advanced Drug Delivery Reviews 19 (1996) 115-130; or H. Bundgaard, Drugs of the Future 16 (1991) 443 which are all incorporated herein by reference. Suitable prodrugs for the compounds of the formula I are especially acyl prodrugs and carbamate prodrugs of acylatable nitrogen-containing groups such as amino groups and the guanidino group and also ester prodrugs and amide prodrugs of carboxylic acid groups which may be present in compounds of the formula I. In the acyl prodrugs and carbamate prodrugs one or more, for example one or two, hydrogen atoms on nitrogen atoms in such groups are replaced with an acyl group or a carbamate, preferably a -(C_1-C_6)-alkyloxycarbonyl group. Suitable acyl groups and carbamate groups for acyl prodrugs and carbamate prodrugs are, for example, the groups R^{p1}-CO- and R^{p2}O-CO-, in which R^{p1} is hydrogen, (C_1-C_{18})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_4)-alkyl-, (C_6-C_{14})-aryl, Het-, (C_6-C_{14})-aryl-(C_1-C_4)-alkyl- or Het-(C_1-C_4)-alkyl- and in which R^{p2} has the meanings indicated for R^{p1} with the exception of hydrogen.

Especially preferred compounds of the formula I, are those wherein two or more residues are defined as indicated before for preferred compounds of the formula I, or residues can have one or some of the specific denotations of the residues given in their general definitions or in the definitions of preferred compounds before. All possible combinations of definitions given for preferred definitions and of specific denotations of residues explicitly are subject of the present invention.

Also with respect to all preferred compounds of the formula I all their stereoisomeric forms and mixtures thereof in any ratio and their physiologically acceptable salts explicitly are a subject of

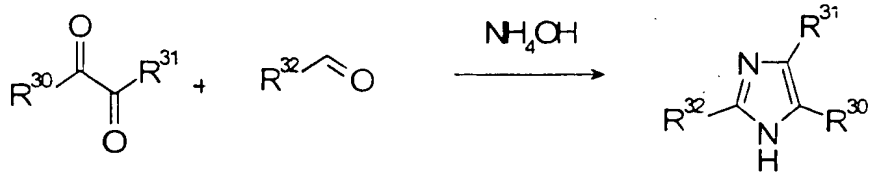
the present invention, as well as are their prodrugs. Similarly, also in all preferred compounds of the formula I, all residues that are present more than one time in the molecule are independent of each other and can be identical or different.

The compounds of the formula I can be prepared by utilising procedures and techniques, which per se are well known and appreciated by one of ordinary skill in the art. Starting materials or building blocks for use in the general synthetic procedures that can be applied in the preparation of the compounds of formula I are readily available to one of ordinary skill in the art. In many cases they are commercially available or have been described in the literature. Otherwise they can be prepared from readily available precursor compounds analogously to procedures described in the literature, or by procedures or analogously to procedures described in this application.

In general, compounds of the formula I can be prepared, for example in the course of a convergent synthesis, by linking two or more fragments which can be derived retrosynthetically from the formula I. More specifically, suitably substituted starting Imidazole derivatives are employed as building blocks in the preparation of the compounds of formula I. If not commercially available, such Imidazole derivatives can be prepared according to the well-known standard procedures for the formation of the Imidazole ring system. By choosing suitable precursor molecules, these imidazole syntheses allow the introduction of a variety of substituents into the various positions of the imidazole system, which can be chemically modified in order to finally arrive at the molecule of the formula I having the desired substituent pattern. As one of the comprehensive reviews in which numerous details and literature references on the chemistry of imidazole and on synthetic procedures for their preparation can be found, M. R. Grimmett in Comprehensive Heterocyclic chemistry; Eds. A. Katritzky, Ch. Rees, E. Scriven; Elsevier 1996, Vol. 3; and K. Ebel in Houben-Weyl, "Methoden der Organischen Chemie" (Methods of Organic Chemistry), Georg Thieme Verlag, Stuttgart, Germany 1994, Vol. E8c Hetarene.

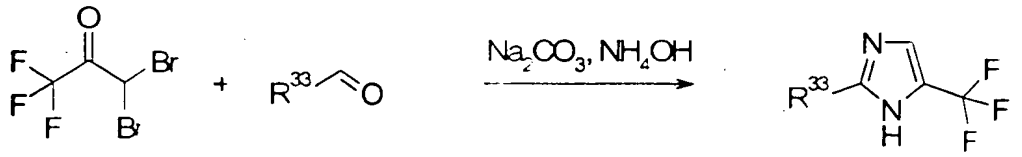
If starting imidazole derivatives are not commercially available and have to be synthesized this can be done, for example, according to the well known imidazole syntheses mentioned above. In the following procedures of particuluar interest for the embodiment of this invention are explained briefly, however, they are standard procedures comprehensively discussed in the literature, and are well known to one skilled in the art.

One cyclisation reaction to the imidazole core 4 starts from a 1,2- diketo fragment **2** and an aldehyde **3** in the presence of an ammonia source (K. Wenger et al., Arch. Pharm. 1974, 492; M. Brackeen et al., Tetrahedron Lett. 1994, 1635). Many variations of this reaction are well documented by K. Ebel in Houben-Weyl, "Methoden der Organischen Chemie" (Methods of Organic Chemistry), Georg Thieme Verlag, Stuttgart, Germany 1994, Vol. E8c Hetarene.



2 **3** **4**

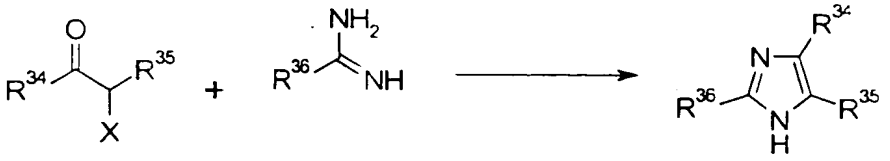
A closely related procedure is the condensation of trifluorodibromoacetone **5** with a wide variety of aldehydes **6** in the presence of ammonia to the corresponding imidazoles **7** (Matthews et al., J. Med. Chem. 1990, 317; J. J. Baldwin et al., J. Med. Chem. 1979, 687; J. J. Baldwin et al., J. Med. Chem. 1975, 895).



5 **6** **7**

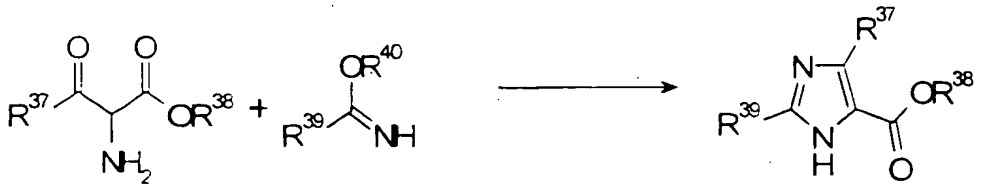
This reaction leads to 4-trifluoroimidazole derivatives **7**, which then, after being optionally derivatisized, can be easily converted into a carboxylic acid or carboxylic ester.

Another method involves the reaction of a α-haloketone (X = Cl, Br) **8** or α-hydroxyketone **8** (X = OH) and an amidine **9** to the corresponding imidazole **10** (J. J. Baldwin et al., J. Med. Chem. 1986, 1065; G. Kempter et al., J. Prakt. Chem. 1971, 977).



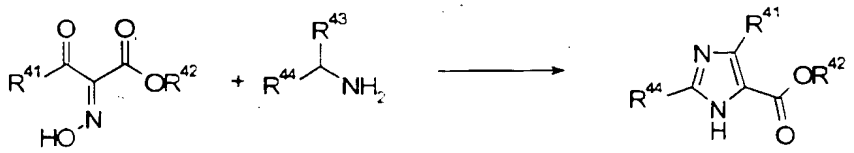
8 **9** **10**

Furthermore 4-carboxyimidazoles **13** can also built up starting from the imidate **12** and and amino-β-ketoester **11**. (D. Judd et al., J. Med. Chem. 1994, 3108).



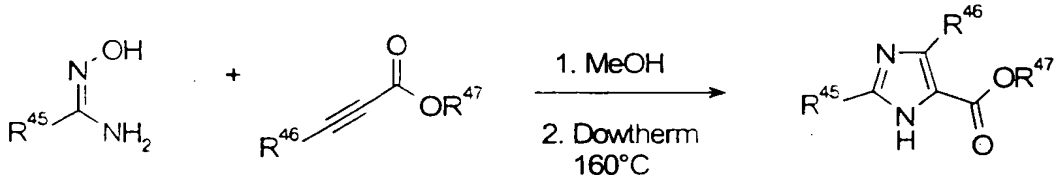
11 12 13

Following a procedure from A. Veronese et al., Synthesis 1985, 300; A. Veronese et al.; J. Heterocyclic. Chem. 1980, 1723, and Raghu et al., US 4,395,547 utilising hydroxyimino-β-ketoesters **14** and activated primary amines **15** (R^{43} = H) or α-aminoacids **15** (R^{43} = COOH) a wide variety of 4-carboxyimidazoles **16** can be synthesised.



14 15 16

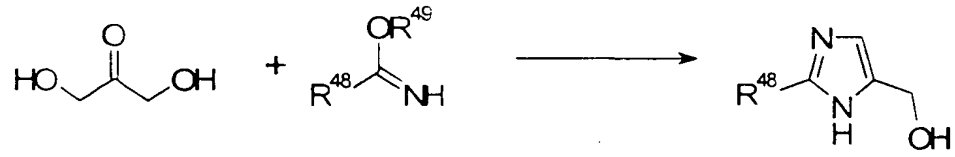
Synthetic access to 4-carboxyimidazoles **19** can also advantageously archieved for example by following a procedure described by N. Heindel et al., Tetrahedron Lett. 1971, 1439 and R. Paul et al., J. Med. Chem. 1985, 1704.



17 18 19

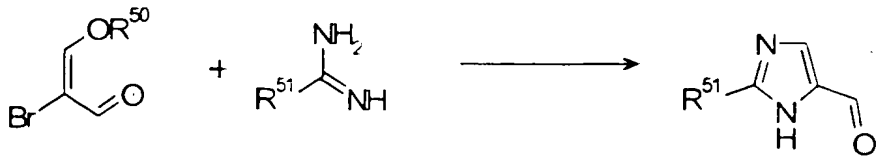
Condensation of the hydroxyamidine **17** with a propynic ester **18** derivative leads after rearrangement and pyrolytic elimination to the desired carboxy imidazoles **19**.

Starting from the imidate **21**, readily available from the corresponding nitrile, a wide range of imidazoles **22** is accessible after reaction with 1,3- dihydroxyacetone **20** (S. Shilcrat et al., J. Org. Chem. 1997, 8449).



20 21 22

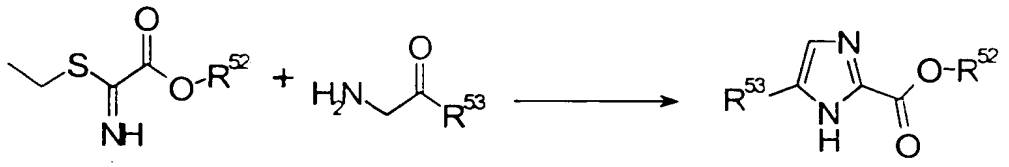
Analogously reaction of amidine **24** with bromoenolether **23** leads to formylimidazoles **25** of type (S. Shilcrat et al., J. Org. Chem. 1997, 8449)



23 **24** **25**

The hydroxymethyl group of **22** as well as the formyl group of **25** can optionally be transformed to a variety of functional groups, for example, by oxidation to the corresponding carboxylic acid or carboxylic ester.

Condensation of ethylthioiminoacetate **26** with α-aminoketones **27** is also a valuable pathway to built up the carboxyimidazoles **28** core (H. Yamanaka et al., Chem. Pharm. Bull. 1983, 31, 4549 and S. Mignani et al., Bioorg. Med. Chem. Lett. 2001, 11, 127).



26 **27** **28**

Depending on the substituents in the starting materials, in certain imidazole syntheses mixtures of positional isomers may be obtained, which, however, can be separated by modern separation techniques like, for example, preparative HPLC.

Further, in order to obtain the desired substituents at the imidazole ring system in the formula I the functional groups introduced into the ring system during the imidazole synthesis can be chemically modified. Especially the groups present in the imidazole ring system can be modified by a variety of reactions and thus the desired residues R^{1a}, R^{1b} be obtained. For example, an imidazole carrying a hydrogen atom in the 2-position can also be obtained by saponification and subsequent decarboxylation of imidazole carrying an ester group in the respective position. Carboxylic acid groups and acetic acid groups in the 2-position, the 4-position and the 5-position can be converted into their homologues by usual reactions for chain elongation of carboxylic acids. Halogen atoms can be introduced into the 2-position, the 4-position and the 5-position, for example according to procedures described in the literature like the following. For the fluorination of imidazoles N-fluoro-2,4,6-trimethylpyridinium triflate is the reagent of choice (T. Umemoto, S. Fukami, G. Tomizawa, K. Harasawa, K. Kawada, K. Tomita, J. Am. Chem. Soc. 1990, 112, 8563) but is not limited to this reagent. The chlorination, bromination, or iodination of

imidazoles can be accomplished by the reaction of the elemental halogens or by the use of NCS, NBS or NIS and many other reagents well known to those skilled in the art. This procedures are for example referred in Y. Shi et al., Synth. Commun. 1993, 23, 2623; H. Rapoport et al., Synthesis 1988, 767; R. Jones et al., J. Org. Chem. 1999, 64, 6575; J. Sessler et al., Chem. Eur. J. 2001, 7, 721. Depending on the reaction conditions, reagent, stochiometry and substitution pattern the halogen is introduced in the 2-position and/or 4-position and/or 5-position. By selective halogen/metal exchange or metalation by selective hydrogen/metal exchange and subsequent reaction with a wide range of electrophiles various substituents can be introduced at the heterocyclic nucleus. (R. Breslow et al., J. Am. Chem. Soc. 1983, 105, 5337; P. Knochel et al., J. Org. Chem. 2000, 65, 4618; S. Ohta et al., Chem. Pharm. Bull. 1996, 44, 1831).

Halogens or hydroxy groups – via the triflate or nonaflate – or primary amines - via its diazonium salt – or after interconversion to the corresponding stannane, or boronic acid - present in the imidazole structure can be converted into a variety of other functional groups like for example –CN, $-CF_3$, $-C_2F_5$, ethers, acids, amides, amines, alkyl- or aryl- groups mediated by means of transition metals, namely palladium or nickel catalysts or copper salts and reagents for example referred to below (F. Diederich, P. Stang, Metal-catalyzed Cross-coupling Reactions, Wiley-VCH, 1998; or M. Beller, C. Bolm, Transition Metals for Organic Synthesis, Wiley-VCH, 1998; J. Tsuji, Palladium Reagents and Catalysts, Wiley, 1996; J. Hartwig, Angew. Chem. 1998, 110, 2154; B. Yang, S. Buchwald, J. Organomet. Chem. 1999, 576, 125; T. Sakamoto, K. Ohsawa, J. Chem. Soc. Perkin Trans I, 1999, 2323; D. Nichols, S. Frescas, D. Marona-Lewicka, X. Huang, B. Roth, G. Gudelsky, J. Nash, J. Med. Chem, 1994, 37, 4347; P. Lam, C. Clark, S. Saubern, J. Adams, M. Winters, D. Chan, A. Combs, Tetrahedron Lett., 1998, 39, 2941; D. Chan, K. Monaco, R. Wang, M. Winters, Tetrahedron Lett. 1998, 39, 2933; V. Farina, V. Krishnamurthy, W. Scott, The Stille Reaction, Wiley, 1994; F. Qing et al. J. Chem. Soc. Perkin Trans. I 1997, 3053; S. Buchwald et al. J. Am. Chem Soc. 2001, 123, 7727; S. Kang et al. Synlett 2002, 3, 427; S. Buchwald et al. Organic Lett. 2002, 4, 581; T. Fuchikami et al. Tetrahedron Lett. 1991, 32, 91; Q. Chen et al. Tetrahedron Lett. 1991, 32, 7689).

For example, nitro groups can be reduced to amino group with various reducing agents, such as sulfides, dithionites, complex hydrides or by catalytic hydrogenation. A reduction of a nitro group may also be carried out at a later stage of the synthesis of a compound of the formula I a reduction of a nitro group to an amino group may also occur simultaneously with a reaction performed on another functional group, for example when reacting a group like a cyano group with hydrogen sulfide or when hydrogenating a group. In order to introduce the residues R^{1a}, R^{1b}, amino groups can then be modified according to standard procedures for alkylation, for example by reaction with (substituted) alkyl halogenides or by reductive amination of carbonyl compounds, according to standard procedures for acylation, for example by reaction with

activated carboxylic acid derivatives such as acid chlorides, anhydrides, activated esters or others or by reaction with carboxylic acids in the presence of an activating agent, or according to standard procedures for sulfonylation, for example by reaction with sulfonyl chlorides.

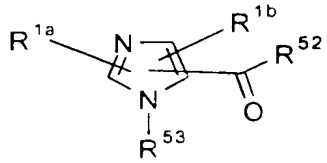
Ester groups present in the imidazole nucleus can be hydrolyzed to the corresponding carboxylic acids, which after activation can then be reacted with amines or alcohols under standard conditions. Ether groups present at the imidazole nucleus, for example benzyloxy groups or other easily cleavable ether groups, can be cleaved to give hydroxy groups which then can be reacted with a variety of agents, for example etherification agents or activating agents allowing replacement of the hydroxy group by other groups. Sulfur-containing groups can be reacted analogously.

During the course of the synthesis in order to modify the groups R^{55} or R^{6} attached to the imidazole ring system by application of parallel synthesis methodology, beside a variety of reactions, palladium, nickel or copper catalysis can be extremely useful. Such reactions are described for example in F. Diederich, P. Stang, Metal-catalyzed Cross-coupling Reactions, Wiley-VCH, 1998; or M. Beller, C. Bolm, Transition Metals for Organic Synthesis, Wiley-VCH, 1998; J. Tsuji, Palladium Reagents and Catalysts, Wiley, 1996; J. Hartwig, Angew. Chem. 1998, 110, 2154; B. Yang, S. Buchwald, J. Organomet. Chem. 1999, 576, 125; P. Lam, C. Clark, S. Saubern, J. Adams, M. Winters, D. Chan, A. Combs, Tetrahedron Lett. 1998, 39, 2941; D. Chan, K. Monaco, R. Wang, M. Winters, Tetrahedron Lett. 1998, 39, 2933; J. Wolfe, H. Tomori, J. Sadight, J. Yin, S. Buchwald, J. Org. Chem. 2000, 65, 1158; V. Farina, V. Krishnamurthy, W. Scott, The Stille Reaction, Wiley, 1994; S. Buchwald et al., J. Am. Chem Soc. 2001, 123, 7727; S. Kang et al., Synlett 2002, 3, 427; S. Buchwald et al., Org. Lett. 2002, 4, 581.

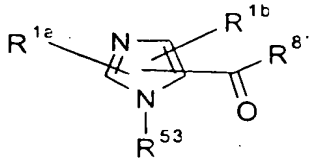
The previously-mentioned reactions for the conversion of functional groups are furthermore, in general, extensively described in textbooks of organic chemistry like M. Smith, J. March, March's Advanced Organic Chemistry, Wiley-VCH, 2001 and in treatises like Houben-Weyl, "Methoden der Organischen Chemie" (Methods of Organic Chemistry), Georg Thieme Verlag, Stuttgart, Germany, or "Organic Reactions", John Wiley & Sons, New York, or R. C. Larock, " Comprehensive Organic Transformations", Wiley-VCH, 2nd ed (1999), B. Trost, I. Fleming (eds.) Comprehensive Organic Synthesis, Pergamon,1991; A. Katritzky, C. Rees, E. Scriven Comprehensive Heterocyclic Chemistry II, Elsevier Science, 1996) in which details on the reactions and primary source literature can be found. Due to the fact that in the present case the functional groups are attached to an imidazole ring it may in certain cases become necessary to specifically adapt reaction conditions or to choose specific reagents from a variety of reagents that can in principle be employed into a

conversion reaction, or otherwise to take specific measures for achieving a desired conversion, for example to use protection group techniques. However, finding out suitable reaction variants and reaction conditions in such cases does not cause any problems for one skilled in the art. The structural elements present in the residues in the 1-position of the imidazole ring in the compounds of the formula I, the $COR^{8'}$ group present in the 4-position and/or in the 5-position of the imidazole ring can be introduced into the starting imidazole derivative obtainable as outlined above by consecutive reaction steps using parallel synthesis methodologies like those outlines below using procedures which per se are well known to one skilled in the art.

The residues $R^{8'}$ that can be introduced in formula **29**, for example, by condensing a corresponding carboxylic acid of the formula **29** with a compound of the formula $HR^{8'}$, i. e. with an amine of the formula $HN(R^{1'})R^{2'}$–V-G-M to give a compound of the formula **30**. The compound of the formula **30** thus obtained can already contain the desired final groups, i. e. the groups $R^{8'}$ and R^{55} can be the groups $-N(R^1)-R^2$–V-G-M and R^0-Q- as defined in the formula I or optionally in the compound of the formula **30** thus obtained subsequently the residue or the residues $R^{8'}$ and the residue R^{55} are converted into the residues $-N(R^1)-R^2$–V-G-M and R^0-Q- , respectively, to give the desired compound of the formula I.



29



30

$HR^{8'}$ ⟶ formula I

Thus, the residues $R^{8'}$ and the residues $R^{1'}$ and $R^{2'}$–V-G-M contained therein can have the denotations of R^1 and R^2–V-G-M, respectively, given above or in addition in the residues $R^{1'}$ and $R^{2'}$–V-G-M functional groups can also be present in the form of groups that can subsequently be transformed into the final groups R^1 and R^2–V-G-M, i.e. functional groups can be present in the form of precursor groups or of derivatives, for example in protected form. In the course of the preparation of the compounds of the formula I it can generally be advantageous or necessary to introduce functional groups which reduce or prevent undesired reactions or side reactions in the

respective synthesis step, in the form of precursor groups which are later converted into the desired functional groups, or to temporarily block functional groups by a protective group strategy suited to the synthesis problem. Such strategies are well known to those skilled in the art (see, for example, Greene and Wuts, Protective Groups in Organic Synthesis, Wiley, 1991, or P. Kocienski, Protecting Groups, Thieme 1994). As examples of precursor groups nitro groups and cyano groups may be mentioned which can in a later step be transformed into carboxylic acid derivatives or by reduction into aminomethyl groups, or nitro groups which may be transformed by reduction like catalytic hydrogenation into amino groups by reduction. Protective groups can also have the meaning of a solid phase, and cleavage from the solid phase stands for the removal of the protective group. The use of such techniques is known to those skilled in the art (Burgess K (Ed.) Solid Phase Organic Synthesis, New York, Wiley, 2000). For example, a phenolic hydroxy group can be attached to a trityl-polystyrene resin, which serves as a protecting group, and the molecule is cleaved from this resin by treatment with TFA at a later stage of the synthesis.

The residue R^{55} in the compounds of the formulae **29** and **30** can denote the group -Q-R^0 as defined above which finally is to be present in the desired target molecule of the formula I, or it can denote a group which can subsequently be transformed into the group -Q-R^0, for example a precursor group or a derivative of the group -Q-R^0 in which functional groups are present in protected form, or R^{55} can denote a hydrogen atom or a protective group for the nitrogen atom of the imidazole ring. Similarly, the residues R^{1e}, R^{1a} and R^{1b} in the formulae **29** and **30** have the corresponding definitions of R^4, and R^3 in formula I as defined above, however, for the synthesis of the compounds of the formula I these residues, too, can in principle be present at the stage of the condensation of a compound of the formula **29** with a compound of the formula $HR^{8'}$ giving a compound of the formula **30** in the form of precursor groups or in protected form.

The residues R^{54} in the compounds of the formula **29** which can be identical or different, can be, for example, hydroxy or (C_1-C_4)-alkoxy, i. e., the groups COR^{54} present in the compounds of the formula **29** can be, for example, the free carboxylic acids or esters thereof like alkyl esters as can be the groups $COR^{8'}$ in the compounds of the formula I. The groups COR^{54} can also be any other activated derivative of a carboxylic acid which allows amide formation, ester formation or thioester formation with a compound of the formula $HR^{8'}$. The group COR^{54} can be, for example, an acid chloride, an activated ester like a substituted phenyl ester, an azolide like an imidazolide, an azide or a mixed anhydride, for example a mixed anhydride with a carbonic acid ester or with a sulfonic acid, which derivatives can all be prepared from the carboxylic acid by standard procedures and can be reacted with an amine, an alcohol or a mercaptan of the

formula $HR^{8'}$ under standard conditions. A carboxylic acid group COOH representing COR^{54} in a compound of the formula **29** can be obtained, for example, from an ester group introduced into the imidazole system during an imidazole synthesis by standard hydrolysis procedures.

Compounds of the formula I in which a group $COR^{8'}$ is an ester group can also be prepared from compounds of the formula **29** in which COR^{54} is a carboxylic acid group by common esterification reactions like, for example, reacting the acid with an alcohol under acid catalysis, or alkylation of a salt of the carboxylic acid with an electrophile like an alkyl halogenide, or by transesterification from another ester. Compounds of the formula I in which a group $COR^{8'}$ is an amide group can be prepared from amines and compounds of the formula **29** in which COR^{54} is a carboxylic acid group or an ester thereof by common amination reactions. Especially for the preparation of amides the compounds of the formula **29** in which COR^{54} is a carboxylic acid group can be condensed under standard conditions with compounds of the formula $HR^{8'}$ which are amines by means of common coupling reagents used in peptide synthesis. Such coupling reagents are, for example, carbodiimides like dicyclohexylcarbodiimide (DCC) or diisopropylcarbodiimide, carbonyldiazoles like carbonyldiimidazole (CDI) and similar reagents, propylphosphonic anhydride, O-((cyano-(ethoxycarbonyl)-methylene)amino)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TOTU), diethylphosphoryl cyanide (DEPC) or bis-(2-oxo-3-oxazolidinyl)-phosphoryl chloride (BOP-Cl) and many others.

If the residue $-Q-R^0$ present in an imidazole of the formula I or the residue R^{55} present in an imidazole of the formula **29**, or a residue in which functional groups within the residue $-Q-R^0$ or R^{55} are present in protected form or in the form of a precursor group, have not already been introduced during a preceding step, for example during a synthesis of the imidazole nucleus, these residues can, for example, be introduced into the 1-position of the imidazole system by conventional literature procedures well known to one skilled in the art for N-alkylation, reductive amination, N-arylation, N-acylation or N-sulfonylation of ring nitrogen atoms of heterocycles. The starting imidazole derivative that is to be employed in such a reaction carries a hydrogen atom in the 1-position. N-Alkylation of a ring nitrogen atom can, for example, be performed under standard conditions, preferably in the presence of a base like K_2CO_3, Cs_2CO_3, NaH or KO^tBu, using an alkylating compound of the formula $LG-Q-R^0$ or of the formula R^{55}-LG, wherein the atom in the group Q or in the group R^{55} bonded to the group LG in this case is an aliphatic carbon atom of an alkyl moiety and LG is a leaving group, for example halogen like chlorine, bromine or iodine, or a sulfonyloxy group like tosyloxy, mesyloxy or trifluormethylsulfonyloxy. LG may, for example, also be a hydroxy group which, in order to achieve the alkylation reaction, is activated by a conventional activating agent. The

regioselectivity of the N-alkylation can be controlled by the choice of the base, solvent and reaction conditions as for example described by M. Pierce et al., J. Org. Chem. 1993, 58, 4642. Alternatively, a protective group strategy, like for example described by F. Guibé et al., Tetrahedron Lett. 1997, 35, 12525; B. Kim et al., Tetrahedron Lett. 2000, 41, 10031; N. Anthony et al., J. Med. Chem. 1999, 42, 3356 may be useful in order to obtain one regioisomer selectively. Nevertheless mixtures of positional isomers, can be separated by modern separation techniques like, for example, preparative HPLC.

For the preparation of compounds in which A is a direct linkage and an aromatic group is directly bonded to the 1-position of the imidazole system, conventional arylation procedures can be used. For example aryl fluorides like alkyl fluorobenzoates or 4-fluorophenyl methyl sulfones can be employed as arylating agents. Such processes are described, for example, by M. Yamada et al. J. Med. Chem. 1996, 39, 596; J. Ohmori et al. J. Med. Chem. 1996, 39, 3971. Alternatively a wide variety of substituted aryl iodides, aryl bromides or aryl triflates can serve as arylating agents at the 1-position of the heterocyclic nitrogen in a copper salt or palladium mediated reaction according for example to P. Cozzi et al. Farmaco 1987, 42, 205; P. Unangst, D. Connor, R. Stabler, R. Weikert, J. Heterocycl. Chem. 1987, 24, 811; G. Tokmakov, I. Grandberg, Tetrahedron 1995, 51, 2091; D. Old, M. Harris, S. Buchwald, Org. Lett. 2000, 2, 1403, G. Mann, J. Hartwig, M. Driver, C. Fernandez-Rivas, J. Am. Chem. Soc. 1998, 120, 827; J. Hartwig, M. Kawatsura, S. Hauk, K. Shaughnessy, L. J. Org. Chem. 1999, 64, 5575; S. Buchwald et al., J. Am. Chem. Soc. 2001, 123, 7727. Moreover such arylations can also be accomplished by reaction of a wide range of substituted aryl boronic acids as demonstrated for example by W. Mederski, M. Lefort, M. Germann, D. Kux, Tetrahedron 1999, 55, 12757; J. Collman et al., J. Org. Chem. 2001, 66, 7892.

Preferred methods include, but are not limited to those described in the examples.

The compounds of the present invention are serine protease inhibitors, which inhibit the activity of the blood coagulation enzyme factors Xa and/or factor VIIa. In particular, they are highly active inhibitors of factor Xa. They are specific serine protease inhibitors inasmuch as they do not substantially inhibit the activity of other proteases whose inhibition is not desired. The activity of the compounds of the formula I can be determined, for example, in the assays described below or in other assays known to those skilled in the art. With respect to factor Xa inhibition, a preferred embodiment of the invention comprises compounds which have a Ki □ 1 for factor Xa inhibition as determined in the assay described below, with or without concomitant factor VIIa inhibition, and which preferably do not substantially inhibit the activity of other proteases involved in coagulation and fibrinolysis whose inhibition is not desired (using the

same concentration of the inhibitor). The compounds of the invention inhibit factor Xa catalytic activity either directly, within the prothrombinase complex or as a soluble subunit, or indirectly, by inhibiting the assembly of factor Xa into the prothrombinase complex.

The present invention also relates to the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for use as pharmaceuticals (or medicaments), to the use of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for the production of pharmaceuticals for inhibition of factor Xa and/or factor VIIa or for influencing blood coagulation, inflammatory response or fibrinolysis or for the therapy or prophylaxis of the diseases mentioned above or below, for example for the production of pharmaceuticals for the therapy and prophylaxis of cardiovascular disorders, thromboembolic diseases or restenoses. The invention also relates to the use of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for the inhibition of factor Xa and/or factor VIIa or for influencing blood coagulation or fibrinolysis or for the therapy or prophylaxis of the diseases mentioned above or below, for example for use in the therapy and prophylaxis of cardiovascular disorders, thromboembolic diseases or restenoses, and to methods of treatment aiming at such purposes including methods for said therapies and prophylaxis. The present invention also relates to pharmaceutical preparations (or pharmaceutical compositions) which contain an effective amount of at least one compound of the formula I and/or its physiologically tolerable salts and/or its prodrugs in addition to a customary pharmaceutically acceptable carrier, i. e. one or more pharmaceutically acceptable carrier substances or excipients and/or auxiliary substances or additives.

The invention also relates to the treatment of disease states such as abnormal thrombus formation, acute myocardial infarction, unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy or percutaneous transluminal coronary angioplasty, transient ischemic attacks, stroke, pathologic thrombus formation occurring in the veins of the lower extremities following abdominal, knee and hip surgery, a risk of pulmonary thromboembolism, or disseminated systemic intravascular coagulatopathy occurring in vascular systems during septic shock, certain viral infections or cancer.

The compounds of the formula I and their physiologically tolerable salts and their prodrugs can be administered to animals, preferably to mammals, and in particular to humans as pharmaceuticals for therapy or prophylaxis. They can be administered on their own, or in mixtures with one another or in the form of pharmaceutical preparations, which permit enteral or parenteral administration.

The pharmaceuticals can be administered orally, for example in the form of pills, tablets, lacquered tablets, coated tablets, granules, hard and soft gelatin capsules, solutions, syrups, emulsions, suspensions or aerosol mixtures. Administration, however, can also be carried out rectally, for example in the form of suppositories, or parenterally, for example intravenously, intramuscularly or subcutaneously, in the form of injection solutions or infusion solutions, microcapsules, implants or rods, or percutaneously or topically, for example in the form of ointments, solutions or tinctures, or in other ways, for example in the form of aerosols or nasal sprays.

The pharmaceutical preparations according to the invention are prepared in a manner known per se and familiar to one skilled in the art, pharmaceutically acceptable inert inorganic and/or organic carriers being used in addition to the compound(s) of the formula I and/or its (their) physiologically tolerable salts and/or its (their) prodrugs. For the production of pills, tablets, coated tablets and hard gelatin capsules it is possible to use, for example, lactose, cornstarch or derivatives thereof, talc, stearic acid or its salts, etc. Carriers for soft gelatin capsules and suppositories are, for example, fats, waxes, semisolid and liquid polyols, natural or hardened oils, etc. Suitable carriers for the production of solutions, for example injection solutions, or of emulsions or syrups are, for example, water, saline, alcohols, glycerol, polyols, sucrose, invert sugar, glucose, vegetable oils, etc. Suitable carriers for microcapsules, implants or rods are, for example, copolymers of glycolic acid and lactic acid. The pharmaceutical preparations normally contain about 0.5 % to 90 % by weight of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs. The amount of the active ingredient of the formula I and/or its physiologically tolerable salts and/or its prodrugs in the pharmaceutical preparations normally is from about 0.5 mg to about 1000 mg, preferably from about 1 mg to about 500 mg.

In addition to the active ingredients of the formula I and/or their physiologically acceptable salts and/or prodrugs and to carrier substances, the pharmaceutical preparations can contain additives such as, for example, fillers, disintegrants, binders, lubricants, wetting agents, stabilizers, emulsifiers, preservatives, sweeteners, colorants, flavorings, aromatizers, thickeners, diluents, buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants. They can also contain two or more compounds of the formula I, and/or their physiologically tolerable salts and/or their prodrugs. In case a pharmaceutical preparation contains two or more compounds of the formula I, the selection of the individual compounds can aim at a specific overall pharmacological profile of the pharmaceutical preparation. For example, a highly potent compound with a shorter

duration of action may be combined with a long-acting compound of lower potency. The flexibility permitted with respect to the choice of substituents in the compounds of the formula I allows a great deal of control over the biological and physico-chemical properties of the compounds and thus allows the selection of such desired compounds. Furthermore, in addition to at least one compound of the formula I and/or a physiologically tolerable salt and/or its prodrug, the pharmaceutical preparations can also contain one or more other therapeutically or prophylactically active ingredients.

As inhibitors of factor Xa and/or factor VIIa the compounds of the formula I and their physiologically tolerable salts and their prodrugs are generally suitable for the therapy and prophylaxis of conditions in which the activity of factor Xa and/or factor VIIa plays a role or has an undesired extent, or which can favorably be influenced by inhibiting factor Xa and/or factor VIIa or decreasing their activities, or for the prevention, alleviation or cure of which an inhibition of factor Xa and/or factor VIIa or a decrease in their activity is desired by the physician. As inhibition of factor Xa and/or factor VIIa influences blood coagulation and fibrinolysis, the compounds of the formula I and their physiologically tolerable salts and their prodrugs are generally suitable for reducing blood clotting, or for the therapy and prophylaxis of conditions in which the activity of the blood coagulation system plays a role or has an undesired extent, or which can favorably be influenced by reducing blood clotting, or for the prevention, alleviation or cure of which a decreased activity of the blood coagulation system is desired by the physician. A specific subject of the present invention thus are the reduction or inhibition of unwanted blood clotting, in particular in an individual, by administering an effective amount of a compound I or a physiologically tolerable salt or a prodrug thereof, as well as pharmaceutical preparations therefor.

Conditions in which compounds of the formula I can be favorably used include, for example, cardiovascular disorders, thromboembolic diseases or complications associated, for example, with infection or surgery. The compounds of the present invention can also be used to reduce an inflammatory response. Examples of specific disorders for the treatment or prophylaxis of which the compounds of the formula I can be used are coronary heart disease, myocardial infarction, angina pectoris, vascular restenosis, for example restenosis following angioplasty like PTCA, adult respiratory distress syndrome, multi-organ failure, stroke and disseminated intravascular clotting disorder. Examples of related complications associated with surgery are thromboses like deep vein and proximal vein thrombosis, which can occur following surgery. In view of their pharmacological activity the compounds of the invention can replace or supplement other anticoagulant agents such as heparin. The use of a compound of the invention can result, for

example, in a cost saving as compared to other anticoagulants. When using the compounds of the formula I the dose can vary within wide limits and, as is customary and is known to the physician, is to be suited to the individual conditions in each individual case. It depends, for example, on the specific compound employed, on the nature and severity of the disease to be treated, on the mode and the schedule of administration, or on whether an acute or chronic condition is treated or whether prophylaxis is carried out. An appropriate dosage can be established using clinical approaches well known in the medical art. In general, the daily dose for achieving the desired results in an adult weighing about 75 kg is from 0.01 mg/kg to 100 mg/kg, preferably from 0.1 mg/kg to 50 mg/kg, in particular from 0.1 mg/kg to 10 mg/kg, (in each case in mg per kg of body weight). The daily dose can be divided, in particular in the case of the administration of relatively large amounts, into several, for example 2, 3 or 4, part administrations. As usual, depending on individual behavior it may be necessary to deviate upwards or downwards from the daily dose indicated.

A compound of the formula I can also advantageously be used as an anticoagulant outside an individual. For example, an effective amount of a compound of the invention can be contacted with a freshly drawn blood sample to prevent coagulation of the blood sample. Further, a compound of the formula I and its salts can be used for diagnostic purposes, for example in in vitro diagnoses, and as an auxiliary in biochemical investigations. For example, a compound of the formula I can be used in an assay to identify the presence of factor Xa and/or factor VIIa or to isolate factor Xa and/or factor VIIa in a substantially purified form. A compound of the invention can be labeled with, for example, a radioisotope, and the labeled compound bound to factor Xa and/or factor VIIa is then detected using a routine method useful for detecting the particular label. Thus, a compound of the formula I or a salt thereof can be used as a probe to detect the location or amount of factor Xa and/or factor VIIa activity in vivo, in vitro or ex vivo.

Furthermore, the compounds of the formula I can be used as synthesis intermediates for the preparation of other compounds, in particular of other pharmaceutical active ingredients, which are obtainable from the compounds of the formula I, for example by introduction of substituents or modification of functional groups.

The general synthetic sequences for preparing the compounds useful in the present invention our outlined in the examples given below. Both an explanation of, and the actual procedure for, the various aspects of the present invention are described where appropriate. The following examples are intended to be merely illustrative of the present invention, and not limiting thereof in either scope or spirit. Those with skill in the art will readily understand that known

variations of the conditions and processes described in the examples can be used to synthesize the compounds of the present invention.

It is understood that changes that do not substantially affect the activity of the various embodiments of this invention are included within the invention disclosed herein. Thus, the following examples are intended to illustrate but not limit the present invention.

Examples

When in the final step of the synthesis of a compound an acid such as trifluoroacetic acid or acetic acid was used, for example when trifluoroacetic acid was employed to remove a tBu group or when a compound was purified by chromatography using an eluent which contained such an acid, in some cases, depending on the work-up procedure, for example the details of a freeze-drying process, the compound was obtained partially or completely in the form of a salt of the acid used, for example in the form of the acetic acid salt or trifluoroacetic acid salt or hydrochloric acid salt.

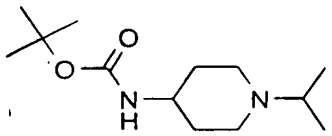
Abbreviations used:

tert-Butyl	tBu
2,2'-bis(diphenylphoshino-1,1'-binaphthyl	Binap
Bis-(oxo-3-oxazolidinyl)-phosphoryl chloride	BOP-Cl
dibenzylidenacetone	dba
Dichloromethane	DCM
Diethylphosphoryl cyanide	DEPC
4-Dimethyaminopyridine	DMAP
N,N-Dimethylformamide	DMF
Dimethylsulfoxide	DMSO
1,1'-Bis(diphenylphosphino)ferrocene	DPPF
O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate	HATU
N-Bromosuccinimide	NBS
N-Chlorosuccinimide	NCS
N-Iodosuccinimide	NIS
N-Ethylmorpholine	NEM
Methanol	MeOH
Room temperature 20 °C to 25 °C	RT

Saturated	sat.
Tetrahydrofuran	THF
Trifluoroacetic acid	TFA
O-((Ethoxycarbonyl)cyanomethyleneamino)-N,N,N',N'-tetramethyluronium tetrafluoroborate	TOTU

Example 1: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

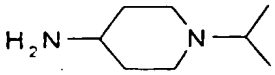
(i) (1-Isopropyl-piperidin-4-yl)-carbamic acid tert-butyl ester



To a solution of 5.0 g Piperidin-4-yl-carbamic acid tert-butyl ester in 15 ml methanol 7.34 ml acetone, 3.14 g $Na(CN)BH_3$ and 0.3 ml acetic acid were added. After stirring for 16 h at RT the solvent was removed under reduced and the residue was partitioned between 30 ml of water and 30 ml ethylacetate. The organic layer was washed with saturated Na_2CO_3 solution, water and then dried over Na_2SO_4. The solvent was removed under reduced pressure and yields a white solid.

Yield: 4.8g MS (ES^+): m/e= 243.

(ii) 1-Isopropyl-piperidin-4-ylamine



To 4.8 g (1-Isopropyl-piperidin-4-yl)-carbamic acid tert-butyl ester in 15 ml methanol, 20 ml methanolic hydrochloric acid (8M) was added and the mixture was stirred for 16 h. Removal of the solvent under reduced pressure yields a white solid, which was coevaporated twicely with 20 ml toluene. The product was obtained as its hydrochloride.

Yield: 5.42 g MS (ES^+): m/e= 143.

(iv) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-imidazole-4-carboxylic acid methyl ester

To a solution of 250 mg 3H-Imidazole-4-carboxylic acid methyl ester in 2 ml DMF 273 mg potassium carbonate and 607 mg 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole [prepared by adopting a procedure described by Ewing, William R.; Becker, Michael R.; Choi-Sledeski, Yong

Mi; Pauls, Heinz W.; He, Wei; Condon, Stephen M.; Davis, Roderick S.; Hanney, Barbara A.; Spada, Alfred P.; Burns, Christopher J.; Jiang, John Z.; Li, Aiwen; Myers, Michael R.; Lau, Wan F.; Poli, Gregory B; PCT Int. Appl. (2001), 460 pp. WO 0107436 A2] were added and the mixture was stirred for 2h at RT. After addition of 5 ml water the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate and then concentrated under reduced pressure. The residue was directly subjected to the subsequent saponification reaction without further purification. Yield: 288 mg

(v) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-imidazole-4-carboxylic acid

To a solution of 720 mg 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-imidazole-4-carboxylic acid methyl ester in 10 ml THF and 3 ml water, 57.0 mg lithium hydroxide monohydrate were added. After stirring for 2 h at 60°C the reaction was cooled to RT. The mixture was acidified with half concentrated hydrochloric acid and the precipitate collected by filtration and washed with 3 ml water. The product was obtained as a white solid which was dried under reduced pressure. Yield: 650 mg

(vi) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

To a solution of 650 mg 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-imidazole-4-carboxylic acid, 1.1 ml N-NEM in 2 ml DCM, 0.7 g TOTU were added and the mixture was stirred for 30 min at RT. Then 0.7 g 1-Isopropyl-piperidin-4-ylamine hydrochloride were added and the reaction was further stirred for 2 h. After addition of 2 ml sat. $NaHCO_3$ the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate and then concentrated under reduced pressure. After removal of the solvent under reduced pressure the residue was purified by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt.

Yield: 74 mg MS (ES^+): m/e = 434, chloro pattern

Example 2: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

This compound was isolated as a by-product in example 2. MS (ES^+): m/e = 434, chloro pattern

Example 3: 5-Chloro-3-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-phenyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 1 with the difference that 5-Chloro-2-phenyl-3H-imidazole-4-carboxylic acid methyl ester was used instead of 3H-Imidazole-4-carboxylic acid methyl ester. MS (ES+): m/e= 544, chloro pattern.

Example 4: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 1 with the difference that 5-Methyl-3H-imidazole-4-carboxylic acid methyl ester was used instead of 3H-Imidazole-4-carboxylic acid methyl ester. MS (ESI+): m/e = 448, chloro pattern.

Example 5: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-ethyl-5-methyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 1 with the difference that 2-Ethyl-5-methyl-3H-imidazole-4-carboxylic acid methyl ester was used instead of 3H-Imidazole-4-carboxylic acid methyl ester. MS (ES+): m/e= 476, chloro pattern.

Example 6: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-ethyl-5-methyl-1H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

This compound was isolated as a by-product in example 5. MS (ES+): m/e = 476, chloro pattern

Example 7: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-iodo-5-methyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

(i) 2-Iodo-5-methyl-3H-imidazole-4-carboxylic acid ethyl ester

A solution of 5 g 5-Methyl-3H-imidazole-4-carboxylic acid ethyl ester and 7.2 g NIS in 50 ml THF were refluxed for 10 h. After cooling, the solvent was removed under reduced pressure and the residue taken-up in ethyl acetate, washed with sat. NaS_2O_3 solution and dried over $MgSO_4$. After removal of the solvent under reduced pressure the product was purified by recrystallisation from ethyl acetate. Yield: 7 g

(ii) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-iodo-5-methyl-3H-imidazole-4-carboxylic acid ethyl ester

To a solution of 500 mg 2-Iodo-5-methyl-3H-imidazole-4-carboxylic acid ethyl ester in 2 ml DMF 1.1 g caesium carbonate and 547 mg 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole [prepared by adopting a procedure described by Ewing, William R.; Becker, Michael R.; Choi-Sledeski, Yong Mi; Pauls, Heinz W.; He, Wei; Condon, Stephen M.; Davis, Roderick S.; Hanney, Barbara A.; Spada, Alfred P.; Burns, Christopher J.; Jiang, John Z.; Li, Aiwen; Myers, Michael R.; Lau, Wan F.; Poli, Gregory B; PCT Int. Appl. (2001), 460 pp. WO 0107436 A2] were added and the mixture was stirred for 2 h at RT. After addition of 5 ml water the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate and then concentrated under reduced pressure. The residue was directly subjected to the subsequent saponification reaction without further purification. Yield: 630 mg

(iii) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-iodo-5-methyl-3H-imidazole-4-carboxylic acid

To a solution of 700 mg 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-iodo-5-methyl-3H-imidazole-4- carboxylic acid ethyl ester in 10 ml THF and 3 ml water 57.0 mg lithium hydroxide monohydrate were added. After stirring for 2 h at 60°C the reaction was cooled to RT and concentrated under reduced pressure. The residue was acidified with half concentrated hydrochloric acid and the precipitate collected by filtration. The product was obtained as a white solid, which was dried under reduced pressure. Yield: 650 mg

(iv) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-iodo-5-methyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

To a solution of 1.5 g 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-iodo-5-methyl-3H-imidazole-4- carboxylic acid, 1.7 ml N-NEM in 10 ml DCM 1.1 g TOTU were added and the mixture was stirred for 30 min at RT. Then 0.7 g 1-Isopropyl-piperidin-4-ylamine hydrochloride were added and the reaction was further stirred for 2 h. After addition of 2 ml sat. $NaHCO_3$ the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate and then concentrated under reduced pressure. After removal of the solvent under reduced pressure the residue was purified by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt.
Yield: 350 mg MS (ES^+): m/e = 574, chloro pattern.

Example 8: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-iodo-5-methyl-1H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

This compound was isolated as a by-product in example 7.
MS (ES+): m/e = 574, chloro pattern.

Example 9: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

(i) N-Hydroxy-2-methoxy-acetamidine

To a solution of 10 g methoxy-acetonitrile, 9.8 g hydroxylamine hydrochloride in 50 ml MeOH 15.8 g KOtBu were added in small portions at RT. After stirring for 5 h the precipitated salts were filtered off and the filtrate was concentrated to yield a white solid, which was used in the next reaction without further purification. Yield: 12 g

(ii) 3-[(2-Methoxy-acetimidoyl)-aminooxy]-acrylic acid methyl ester

To a solution of 1 g N-Hydroxy-2-methoxy-acetamidine in 10 ml MeOH 1.3 ml Propynoic acid methyl ester were added and the mixture heated to 60°C for 3 h. After cooling, the reaction mixture was concentrated under reduced pressure to yield a brown solid, which was used in the next reaction without further purification. Yield: 450 mg

(iii) 2-Methoxymethyl-3H-imidazole-4-carboxylic acid methyl ester

A solution of 450 mg 3-[(2-Methoxy-acetimidoyl)-aminooxy]-acrylic acid methyl ester in 2 ml Dowtherm™ was heated at 180 °C for 18 h. After cooling, the dark brown reaction mixture was diluted with 10 ml heptane and the precipitating solid was purified by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a yellow solid. The product was obtained as its trifluoroacetate salt. Yield: 250 mg

(iii) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-3H-imidazole-4-carboxylic acid methyl ester

To a solution of 50 mg 2-Methoxymethyl-3H-imidazole-4-carboxylic acid methyl ester in 1 ml DMF, 95 mg caesium carbonate and 82 mg 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole [prepared by adopting a procedure described by Ewing, William R.; Becker, Michael R.; Choi-Sledeski, Yong Mi; Pauls, Heinz W.; He, Wei; Condon, Stephen M.; Davis, Roderick S.; Hanney, Barbara A.; Spada, Alfred P.; Burns, Christopher J.; Jiang, John Z.; Li, Aiwen; Myers, Michael R.; Lau, Wan F.; Poli, Gregory B; PCT Int. Appl. (2001), 460 pp. WO 0107436 A2] were added and the mixture was stirred for 2 h at RT. After addition of 5 ml water the mixture was filtered

through a chem elut® cartridge by elution with ethyl acetate and then concentrated under reduced pressure. The residue was directly subjected to the subsequent saponification reaction without further purification. Yield: 72 mg.

(iv) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-3H-imidazole-4-carboxylic acid

To a solution of 400 mg 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-3H-imidazole-4- carboxylic acid methyl ester in 5 ml THF and 1 ml water, 10.0 mg lithium hydroxide monohydrate were added. After stirring for 2 h at 60 °C the reaction was cooled to RT and concentrated under reduced pressure. The residue was acidified with half concentrated hydrochloric acid and filtered through a RP-18 cartridge eluting with H_2O/MeCN gradient. The fractions containing the product were evaporated and lyophilized to yield a white solid.
Yield: 320 mg

(v) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

To a solution of 60 mg 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-3H-imidazole-4- carboxylic acid, 85 µl N-NEM in 1 ml DCM, 55 mg TOTU were added and the mixture was stirred for 30 min at RT. Then 34 mg of 1-Isopropyl-piperidin-4-ylamine hydrochloride were added and the reaction was stirred for 2 h. After addition of 2 ml sat. $NaHCO_3$ the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate and then concentrated under reduced pressure. After removal of the solvent under reduced pressure the residue was purified by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt.
Yield: 10 mg MS (ES^+): m/e = 478, chloro pattern.

Example 10: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-1H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

This compound was isolated as a by-product in example 9. MS (ES^+): m/e = 478, chloro pattern.

Example 11: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-cyclopropyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 9 with the difference that cyclopropanecarbonitrile was used instead of methoxy-acetonitrile.
MS (ESI+): m/e =474, chloro pattern.

Example 12: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(2,6-difluoro-phenyl)-3H-imidazole- 4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 9 with the difference that 2,6-Difluoro-benzonitrile was used instead of methoxy-acetonitrile. MS (ESI+): m/e = 546, chloro pattern.

Example 13: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-cyclopentyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 9 with the difference that cyclopentanecarbonitrile was used instead of methoxy-acetonitrile.
MS (ESI+): m/e =502, chloro pattern.

Example 14: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(2-methoxy-ethyl)-3H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 9 with the difference that 3-Methoxy-propionitrile was used instead of methoxy-acetonitrile.
MS (ESI+): m/e =492, chloro pattern.

Example 15: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(2,6-dichloro-phenyl)-3H-imidazole- 4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 9 with the difference that 2,6-Dichloro-benzonitrile was used instead of methoxy-acetonitrile.
MS (ESI+): m/e = 578, chloro pattern.

Example 16: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-isopropyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogouslyto example 9 with the difference that Isobutyronitrile was used instead of methoxy-acetonitrile.
MS (ESI+): m/e = 476, chloro pattern.

Example 17: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-pyridin-2-yl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogouslyto example 9 with the difference that Pyridine-2-carbonitrile was used instead of methoxy-acetonitrile.
MS (ESI+): m/e = 511, chloro pattern.

Example 18: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-2-phenyl-3H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

(i) 5-Methyl-2-phenyl-3H-imidazole-4-carboxylic acid methyl ester

A solution of 150 mg 2-Iodo-5-methyl-3H-imidazole-4-carboxylic acid ethyl ester, 78 mg Phenyl boronic acid and 600 µl 2M aqueous Na_2CO_3 solution in 3 ml DME was purged with argon for 15 min. Then 20 mg $Pd(Ph_3)_4$ were introduced and the reaction mixture heated for 15 min to 150 °C under microwave irradiation (150 W, CEM Discover™ apparatus). After addition of 2 ml of water the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate and then concentrated under reduced pressure. The residue was purified by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. Yield: 103 mg

(ii) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-2-phenyl-3H-imidazole-4-carboxylic acid methyl ester

To a solution of 60 mg 5-Methyl-2-phenyl-3H-imidazole-4-carboxylic acid methyl ester in 1 ml DMF 95 mg caesium carbonate and 82 mg 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole were added and the mixture was stirred for 2 h at 60°C. After addition of 5 ml water the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate and then concentrated

under reduced pressure. The residue was directly subjected to the subsequent saponification reaction without further purification. Yield: 78 mg

(iii) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-2-phenyl-3H-imidazole-4-carboxylic acid

To a solution of 78 mg 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-3H-imidazole-4- carboxylic acid methyl ester in 2 ml THF and 1 ml water, 10 mg lithium hydroxide monohydrate were added. After stirring for 2 h at 60°C the reaction was cooled to RT and concentrated under reduced pressure. The residue was acidified with half concentrated hydrochloric acid to pH 3 and the precipitating white product was collected by filtration and used without further purification. Yield: 50 mg

(iv) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-2-phenyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

To a solution of 50 mg 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-2-phenyl-3H-imidazole-4- carboxylic acid, 65 µl N-NEM in 1 ml DCM 42 mg TOTU were added and the mixture was stirred for 30 min at RT. Then 25 mg of 1-Isopropyl-piperidin-4-ylamine hydrochloride were added and the reaction was stirred for 1 h. After addition of 2 ml sat. $NaHCO_3$ the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate. After removal of the solvent under reduced pressure the residue was purified by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt.

Yield: 8 mg MS (ESI+): m/e = 524, chloro pattern.

Example 19: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-2-phenyl-1H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 18 with the difference that 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-iodo-5-methyl-1H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide was used instead of 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-2-phenyl-3H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide.

MS (ESI+): m/e = 524, chloro pattern.

Example 20: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-pyridin-3-yl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 9 with the difference that Pyridine-3-carbonitrile was used instead of methoxy-acetonitrile.
MS (ESI+): m/e =511, chloro pattern.

Example 21: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(2-methyl-thiazol-4-yl)-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 9 with the difference that 2-Methyl-thiazole-4-carbonitrile was used instead of methoxy-acetonitrile.
MS (ESI+): m/e =531, chloro pattern.

Example 22: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(2-methyl-thiazol-4-yl)-1H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

This compound was isolated as a by-product in example 21.
MS (ESI+): m/e =531, chloro pattern.

Example 23: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-ethanesulfonyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 1 with the difference 2-Ethanesulfonyl-3H-imidazole-4-carboxylic acid ethyl ester was used instead of 3H-Imidazole-4-carboxylic acid methyl ester. MS (ESI+): m/e =526, chloro pattern.

Example 24: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-3H-imidazole-2,4-dicarboxylic acid 2-amide 4-[(1-isopropyl-piperidin-4-yl)-amide]

(i) 2-Cyano-5-methyl-3H-imidazole-4-carboxylic acid ethyl ester
To a solution of 1 g 2-Iodo-5-methyl-3H-imidazole-4-carboxylic acid ethyl ester in 3 ml pyridine 640 mg CuCN were added and the mixture stirred for 3 h at 110°C. Then the pyridine was

removed under reduced pressure and the residue was directly purified by chromatography on silica eluting with DCM/MeOH 97:3. Yield: 494 mg

(ii) 2-Carbamoyl-3-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-3H-imidazole-4-carboxylic acid

A suspension of 194 mg 2-Cyano-5-methyl-3H-imidazole-4-carboxylic acid ethyl ester, 301 mg 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole and 150 mg K_2CO_3 in 2 ml DMF was stirred for 5 h at RT. After addition of 2 ml brine the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate and then concentrated under reduced pressure. The residue was then dissolved in 5 ml THF/MeOH/water 3:1:1 and treated with 30 mg LiOH monohydrate at RT. After removal of the solvent under reduced pressure the residue was taken-up in 5 ml 5 M HCl. The acid precipitated as a brown solid and and was collected by filtration and was dried under reduced pressure. Yield: 280 mg

(iii) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-3H-imidazole-2,4- dicarboxylic acid 2-amide 4-[(1-isopropyl-piperidin-4-yl)-amide]

To a solution of 2-Carbamoyl-3-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-3H-imidazole-4- carboxylic acid, 0.15 ml NEt_3 in 2 ml DMF 70 mg BOP-Cl and 0.7 g 1-Isopropyl-piperidin-4-ylamine hydrochloride were added and the reaction was stirred for 5 h at RT. After addition of 2 ml sat. $NaHCO_3$ the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate. After removal of the solvent under reduced pressure the residue was purified by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt. Yield: 20 mg MS (ES^+): m/e = 491, chloro pattern

Example 25: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-1H-imidazole-2,4-dicarboxylic acid 2-amide 4-[(1-isopropyl-piperidin-4-yl)-amide]

This compound was isolated as a by-product in example 24. MS (ESI+): m/e =491, chloro pattern.

Example 26: 2-Bromo-3-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-3H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 7 with the difference that NBS was used instead of NIS in the initial halogenation step. MS (ESI+): m/e =527, chloro pattern.

Example 27: 2-Bromo-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-1H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

This compound was isolated as a by-product in example 26. MS (ESI+): m/e =527, chloro pattern.

Example 28: 2-(4-Chlorophenyl)-1-[5-(5-chlorothiophen-2-yl)-isoxazol-3-ylmethyl]-1H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

(i) 2-(4-Chloro-phenyl)-3H-imidazole-4-carboxylic acid ethyl ester

1.0 g (5.9 mmol) of 4-chloro-N-hydroxy-benzamidine and 776 mg (7.96 mmol) of propynoic acid ethyl ester were dissolved in methanol and the resulting solution was boiled under reflux for 15 h. The solvent was removed under reduced pressure, and the residue was dissolved in Dowtherm A. This solution was heated to 190 °C for 2.5 h, allowed to cool, then poured into n-heptane. The precipitated product was collected by filtration and washed with n-heptane.

Yield: 759 mg MS (LCMS-ES+): m/e = 251, chloro pattern.

(ii) 2-(4-Chloro-phenyl)-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-imidazole-4-carboxylic acid ethyl ester

500 mg (2.0 mmol) of 2-(4-Chlorophenyl)-3H-imidazole-4-carboxylic acid ethyl ester was dissolved in 5 ml of DMF and 2.6 g (8 mmol) of cesium carbonate were added at RT. After stirring for 15 min, 445 mg (1.6 mmol) of 3-bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole were added. The reaction was stirred at room temperature for 16 h. The reaction solution was filtered and the product was purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). After lyophilization the product was obtained as a white solid.

Yield: 480 mg MS (LCMS-ES+): m/e = 448.

(iii) 2-(4-Chlorophenyl)-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-imidazole-4-carboxylic acid

480 mg (1.1 mg) of 2-(4-Chloro-phenyl)-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-imidazole-4- carboxylic acid ethyl ester was dissolved in 10 ml of dioxan and 10 ml of 2 N aqueous NaOH was added. The solution was stirred at 60°C for 3 h. The solution was poured into water and the pH was adjusted to 3 by the addition of 2 N aqueous HCl. The precipitated product was filtered off and dried.

Yield: 258 mg MS (LCMS-ES+): m/e = 420.

(iv) 2-(4-Chlorophenyl)-1-[5-(5-chlorothiophen-2-yl)-isoxazol-3-ylmethyl]-1H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

50 mg (0.12 mmol) of 2-(4-Chlorophenyl)-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-imidazole-4- carboxylic acid was dissolved in 3 ml of DMF and 39 mg (0.12 mmol) of TOTU and 0.15 ml (1.2 mmol) of NEM was added. This solution was stirred at room temperature for 30 min. 25.6 mg (0.12 mmol) of 1-isopropyl-piperidin-4-ylamine dihydrochloride was added and the resulting solution was stirred at room temperature for 16 h. The product was purified by preparative RP-HPLC eluting with a gradient of 0 % to 100% acetonitrile in water (added 0.01% trifluoroacetic acid). After lyophilization the product was obtained as its trifluoroacetate salt.

Yield 39.8 mg. MS (LCMS-ES+): m/e = 544 (M+H+).

Example 29: 3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-3H-imidazole-4-carboxylic acid (1-isopropyl- piperidin-4-yl)-amide

(i) 2-Bromo-N-(5-chloro-pyridin-2-yl)-acetamide

To a solution of 5 g 5-Chloro-pyridin-2-ylamine and 1.5 ml pyridine in 30 ml toluene 8 g bromo-acetyl bromide dissolved in 10 ml toluene was added dropwise under ice cooling. After 2 h the precipitate was isolated by filtration and recristallized from toluene to yield a white solid.

Yield: 12 g

(ii) 3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-3H-imidazole-4-carboxylic acid

A suspension of 200 mg 3H-Imidazole-4-carboxylic acid methyl ester, 396 mg), 2-Bromo-N-(5-chloro-pyridin-2-yl)-acetamide and 220 mg K_2CO_3 in 2 ml DMF was stirred for 16 h at RT. The solvent was removed under reduced pressure and the precipitate dissolved in 5 ml THF/water 2:1. Then, 1.5 ml KOH 10% was added at RT and the reaction mixture was stirred for 16 h. Finally, 3 ml of halfconcentrated hydrochloric acid was added to precipitate the acid as a white solid. Yield: 260 mg

(iii) 3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

To a solution of 3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-3H-imidazole-4-carboxylic acid, 0.1 ml NEt_3 in 1 ml DMF 45 mg BOP-Cl and 39 mg 1-Isopropyl-piperidin-4-ylamine hydrochloride were added and the reaction was stirred for 16 h. After addition of 2 ml sat. $NaHCO_3$ the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate. After removal of the solvent under reduced pressure the residue was purified by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt.

Yield: 80 mg MS (ES^+): m/e = 405, chloro pattern.

Example 30: 3-[(4-Chloro-phenylcarbamoyl)-methyl]-2-methoxymethyl-3H-imidazole-4-carboxylic acid (1- isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 29 with the difference that 2-Bromo-N-(4-chloro-phenyl)-acetamide and 2-Methoxymethyl-3H-imidazole-4-carboxylic acid methyl ester were used instead of 2-Bromo-N-(5-chloro-pyridin-2-yl)-acetamide and 3H-Imidazole-4-carboxylic acid methyl ester in the alkylation step.

MS (ESI+): m/e =448, chloro pattern.

Example 31: 1-[(4-Chloro-phenylcarbamoyl)-methyl]-2-methoxymethyl-1H-imidazole-4-carboxylic acid (1- isopropyl-piperidin-4-yl)-amide

This compound was isolated as a by-product in example 30. MS (ESI+): m/e =448, chloro pattern.

Example 32: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-ethanesulfonyl-1H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 29 with the difference that 2-ethanesulfonyl-3H-imidazole-4-carboxylic acid ethyl ester was used instead of 3H-imidazole-4-carboxylic acid methyl ester. MS (ESI+): m/e =497, chloro pattern.

Example 33: 5-Chloro-3-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]-2-phenyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 29 with the difference that 5-Chloro-2-phenyl-3H-imidazole-4-carboxylic acid methyl ester was used instead of 3H-Imidazole-4-carboxylic acid methyl ester. MS (ESI+): m/e =515, chloro pattern.

Example 34: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-cyclopropyl-1H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

This compound was isolated as a by-product in example 11. MS (ESI+): m/e =474, chloro pattern.

Example 35: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(2-methoxy-phenyl)-5-methyl-3H- imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 18 with the difference that 2-methoxyphenyl boronic acid was used instead of phenyl boronic acid.
MS (ESI+): m/e = 555, chloro pattern.

Example 36: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(3-trifluoromethyl-phenyl)-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 9 with the difference that 3-trifluoromethyl-benzonitrile was used instead of methoxy-acetonitrile.
MS (ESI+): m/e = 579, chloro pattern.

Pharmacological testing

The ability of the compounds of the formula I to inhibit factor Xa or factor VIIa or other enzymes like thrombin, plasmin, or trypsin can be assessed by determining the concentration of the compound of the formula I that inhibits enzyme activity by 50 %, i. e. the IC50 value, which was related to the inhibition constant Ki. Purified enzymes were used in chromogenic assays. The concentration of inhibitor that causes a 50 % decrease in the rate of substrate hydrolysis was

determined by linear regression after plotting the relative rates of hydrolysis (compared to the uninhibited control) versus the log of the concentration of the compound of formula I. For calculating the inhibition constant Ki, the IC50 value was corrected for competition with substrate using the formula

$$Ki = IC50 / \{1 + (\text{substrate concentration} / Km)\}$$

wherein Km is the Michaelis-Menten constant (Chen and Prusoff, Biochem. Pharmacol. 22 (1973), 3099-3108; I. H. Segal, Enzyme Kinetics, 1975, John Wiley & Sons, New York, 100-125; which were incorporated herein by reference).

a) Factor Xa Assay

In the assay for determining the inhibition of factor Xa activity TBS-PEG buffer (50 mM Tris-HCl, pH 7.8, 200 mM NaCl, 0.05 % (w/v) PEG-8000, 0.02 % (w/v) NaN3) was used. The IC50 was determined by combining in appropriate wells of a Costar half-area microtiter plate 25 µl human factor Xa (Enzyme Research Laboratories, Inc.; South Bend, Indiana) in TBS-PEG; 40 µl 10 % (v/v) DMSO in TBS-PEG (uninhibited control) or various concentrations of the compound to be tested diluted in 10 % (v/v) DMSO in TBS-PEG; and substrate S-2765 (N(α)-benzyloxycarbonyl-D-Arg-Gly-L-Arg-p-nitroanilide; Kabi Pharmacia, Inc.; Franklin, Ohio) in TBS-PEG.

The assay was performed by pre-incubating the compound of formula I plus enzyme for 10 min. Then the assay was initiated by adding substrate to obtain a final volume of 100 µl. The initial velocity of chromogenic substrate hydrolysis was measured by the change in absorbance at 405 nm using a Bio-tek Instruments kinetic plate reader (Ceres UV900HDi) at 25 °C during the linear portion of the time course (usually 1.5 min after addition of substrate). The enzyme concentration was 0.5 nM and substrate concentration was 140 µM.

b) Factor VIIa Assay

The inhibitory activity towards factor VIIa/tissue factor activity was determined using a chromogenic assay essentially as described previously (J. A. Ostrem et al., Biochemistry 37 (1998) 1053-1059 which was incorporated herein by reference). Kinetic assays were conducted at 25 °C in half-area microtiter plates (Costar Corp., Cambridge, Massachusetts) using a kinetic plate reader (Molecular Devices Spectramax 250). A typical assay consisted of 25 µl human factor VIIa and TF (5 nM and 10 nM, respective final concentration) combined with 40 µl of inhibitor dilutions in 10% DMSO/TBS-PEG buffer (50 mM Tris, 15 mM NaCl, 5 mM $CaCl_2$, 0.05 % PEG 8000, pH 8.15). Following a 15 minute preincubation period, the assay was initiated by the addition of 35 µl of the chromogenic substrate S-2288 (D-Ile-Pro-Arg-p-nitroanilide, Pharmacia Hepar Inc., 500 µM final concentration). The results (inhibition constants Ki (FXa) for inhibition of factor Xa) are shown in Table 1.

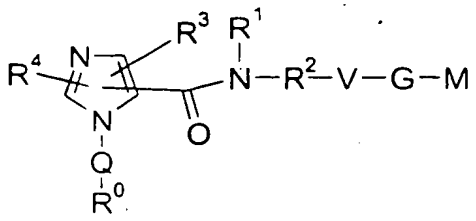
Table1:

Example	Ki(FXa) [μM]	Example	Ki(FXa) [μM]	Example	Ki(FXa) [μM]
1	0.065	14	0.401	24	0.022
3	0.007	15	0.056	26	0.003
5	0.027	16	0.254	29	0.140
6	0.530	17	0.112	30	0.035
7	0.001	18	0.007	33	0.103
9	0.086	20	0.358		
11	0.004	21	0.243		
12	0.018	23	0.006		

5

Patent Claims DEAV2002/0085

1. A compound of the formula I,



(I)

wherein

R^0 is 1) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8,

2) a monocyclic or bicyclic 4- to 15-membered heteroaryl out of the group pyridyl, pyrimidinyl, indolyl, isoindolyl, indazolyl, phthalazinyl, quinolyl, isoquinolyl, benzothiophen, quinazolinyl and phenylpyridyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, or

3) a monocyclic or bicyclic 4- to 15-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, and which is additionally substituted by a monocyclic or bicyclic 4- to 15-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

R8 is 1) halogen,

2) $-NO_2$,

3) -CN,

4) $-C(O)-NH_2$,

5) -OH,

6) $-NH_2$,

7) $-O-CF_3$

8) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by halogen or $-O-(C_1-C_8)$-alkyl,

9) -(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue, or

10) –O-(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,

11) -SO_2-CH_3 or

12) –SO_2-CF_3,

provided that R8 is at least one halogen, -C(O)-NH_2 or –O-(C_1-C_8)-alkyl residue, if R^0 is a monocyclic or bicyclic 6- to 14-membered aryl,

Q is a direct bond, -(C_0 –C_2)-alkylene-C(O)-NR^{10}-, -NR^{10}-C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, -(C_1-C_6)-alkylene, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-S-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-CH(OH)-$(CH_2)_n$-, -$(CH_2)_m$-O-C(O)-NR^{10}-$(CH_2)_n$-, -(C_2-C_3)-alkylene-O-(C_0-C_3)-alkylene-, -(C_2-C_3)-alkylene-S(O)-, -(C_2-C_3)-alkylene-$S(O)_2$-, -$(CH_2)_m$-NR^{10}-C(O)-O-$(CH_2)_n$-, -(C_2-C_3)-alkylene-$S(O)_2$-NH-(R^{10})-, -(C_2-C_3)-alkylene-N(R^{10})- or -(C_0-C_3)-alkylene-C(O)-O- ,

wherein R^{10} is as defined below, and wherein n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6, wherein the alkylene residues which are formed by -$(CH_2)_m$- or -$(CH_2)_n$- are unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -NH_2 or –OH; or

–(C_3-C_6)-cycloalkylen, wherein cycloalkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -NH_2 or –OH;

R^1 is a hydrogen atom, -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13; -(C_1-C_3)-alkylene-C(O)-NH-R^0, -(C_1-C_3)-alkylene-C(O)-O-R15, a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8, wherein R8 is as defined above; a monocyclic or bicyclic 4- to 15-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen; -(C_1-C_3)-perfluoroalkylene,

-(C_1-C_3)-alkylene-S(O)-(C_1-C_4)-alkyl, -(C_1-C_3)-alkylene-S(O)$_2$-(C_1-C_3)-alkyl, -(C_1-C_3)-alkylene-S(O)$_2$-N($R^{4'}$)-$R^{5'}$, -(C_1-C_3)-alkylene-O-(C_1-C_4)-alkyl, -(C_0-C_3)-alkylene-(C_3-C_8)-cycloalkyl, or -(C_0-C_3)-alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, whereas R14 is defined below,

$R^{4'}$ and $R^{5'}$ are independent of one another are identical or different and are hydrogen atom or -(C_1-C_4)-alkyl,

R^2 is a direct bond or –(C_1-C_4)-alkylene, or

R^1 and R^3 together with the atoms to which they are bonded form a 4- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

R^1-N-R^2-V form a 4- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is halogen, -OH, =O, -(C_1-C_8)-alkyl, -(C_1-C_4)-alkoxy, -NO_2, -C(O)-OH, -CN, -NH_2, -C(O)-O-(C_1-C_4)-alkyl, -(C_1-C_8)-alkylsulfonyl, -SO_2, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-N-[(C_1-C_8)-alkyl]$_2$, -NR^{18}-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH_2, –S-R^{18}, or –NR^{18}-C(O)-NH-[(C_1-C_8)-alkyl]$_2$,

wherein R^{18} is hydrogen atom, -(C_1-C_3)-perfluoroalkyl or –(C_1-C_6)-alkyl,

V is 1) a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

2) a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or

3) a monocyclic or bicyclic 4- to 15-membered heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

G is a direct bond, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-CH(OH)-(CH_2)_n-$, $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n-$, $-(CH_2)_m-C(O)-(CH_2)_n-$, $-(CH_2)-S-(CH_2)_n-$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n-$ or $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$,

n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

R^{10} is hydrogen atom, $-(C_1-C_3)$-perfluoroalkyl or $-(C_1-C_6)$-alkyl,

M is 1) a hydrogen atom,

2) $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

3) -C(O)-N(R11)-R12,

4) $-(CH_2)_m-NR^{10}$,

5) $-(C_6-C_{14})$-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

6) $-(C_4-C_{15})$-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

7) $-(C_3-C_8)$-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

8) a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, wherein R14 is defined above,

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,

2) -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

3) -(C_6-C_{14})-aryl-(C_1-C_4)-alkyl-, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13,

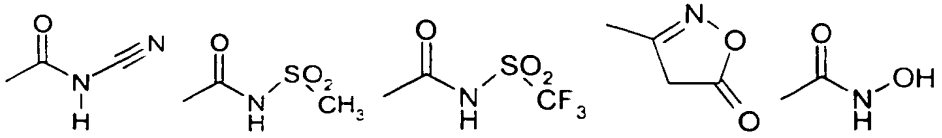
4) -(C_6-C_{14})-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

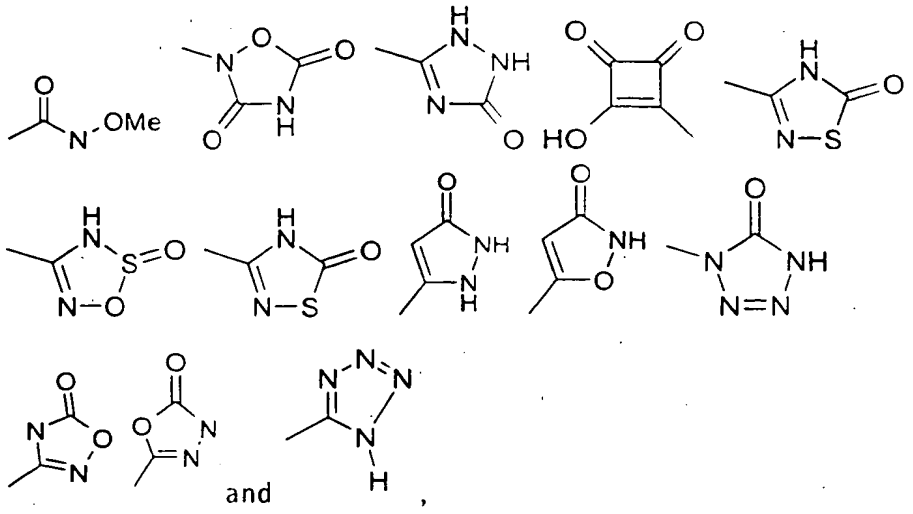
5) -(C_4-C_{15})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13 or

6) -(C_4-C_{15})-heteroaryl-(C_1-C_4)-alkyl-, wherein alkyl and heteroaryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13, or

R11 and R12 together with the nitrogen atom to which they are bonded form a saturated 4- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

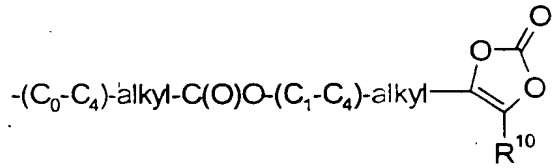
R13 is halogen, -NO_2, -CN, =O, -OH, -(C_1-C_8)-alkyl, -(C_1-C_8)-alkoxy, -CF_3, phenyl, phenyloxy-, -C(O)-O-R^{11}, phenyl-(C_1-C_4)-alkoxy-, -C(O)-N(R^{11})-R^{12}, -N(R^{11})-R^{12}, -NR^{10}-SO_2-R^{10}, -S-R^{10}, -SO_r-R^{10}, wherein r is 1 or 2; -SO_2-N(R^{11})-R^{12}, -C(O)-R^{10}, -(C_0-C_4)-alkyl-C(O)-O-C(R15, R16)-O-C(O)-R17, -(C_0-C_4)-alkyl-C(O)-O-C(R15, R16)-O-C(O)-O-R17, -(C_1-C_4)-perfluoroalkyl, -CN, -O-R15, -O-CF_3, -C(O)-O-R15, -C(O)-H, -NH-C(O)-NH-R^{10}, -NH-C(O)-O-R15, -S(O)-(C_1-C_6)-alkyl, -$S(O)_2$-(C_1-C_6)-alkyl, -$S(O)_2$- N(R^{10})-R^{11}, -(C_1-C_3)-alkylene-O-(C_1-C_3)-alkyl, -NO_2, or a residue from the following list





and ,

or a residue of formula Va,



Va

wherein R10, R11 and R12 are as defined above and R15, R16 and R17 are as defined below,

R15 and R16 are independently of one another hydrogen, -(C_1-C_6)-alkyl, or together with the carbon atom to which they are bonded they can form a 3- to 6 membered carbocyclic ring which is unsubstituted or substituted one to three times by R^{10},

R17 is -(C_1-C_6)-alkyl, -(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-(C_3-C_8)-cycloalkyl wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by R^{10}, and

R^3 and R^4 are independent of one another are identical or different and are

1) hydrogen atom,
2) halogen,
3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13,
4) -(C_1-C_3)-perfluoroalkyl,
5) phenyl, wherein phenyl is unsubstituted or substituted one to three times by R13,

6) -O-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13,

7) $-NO_2$,

8) -CN,

9) -OH,

10) phenyloxy-, wherein phenyloxy is unsubstituted or substituted one to three times by R13,

11) benzyloxy-, wherein benzyloxy is unsubstituted or substituted one to three times by R13,

12) -C(O)-O-R11,

13) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{12} ,

14) -N(R^{11})-R^{12},

15) -NR^{10}-SO_2-R^{10},

16) -S-R^{10},

17) -SO_s-R^{10}, wherein s is 1 or 2,

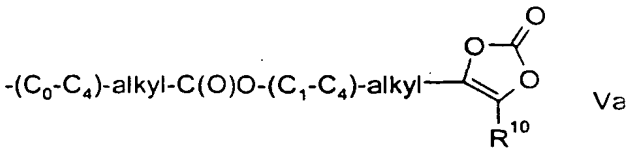
18) -SO_2- N(R^{11})-R^{12},

19) -C(O)-R^{10}, wherein R^{10} is as defined above,

20) -C(O)-O-C(R15, R16)-O-C(O)-R17, wherein R15, R16 and R17 are as defined above,

21) -C(O)-O- C(R15, R16)-O-C(O)-O-R17, wherein R15, R16 and R17 are as defined above,

22) a residue of formula Va,



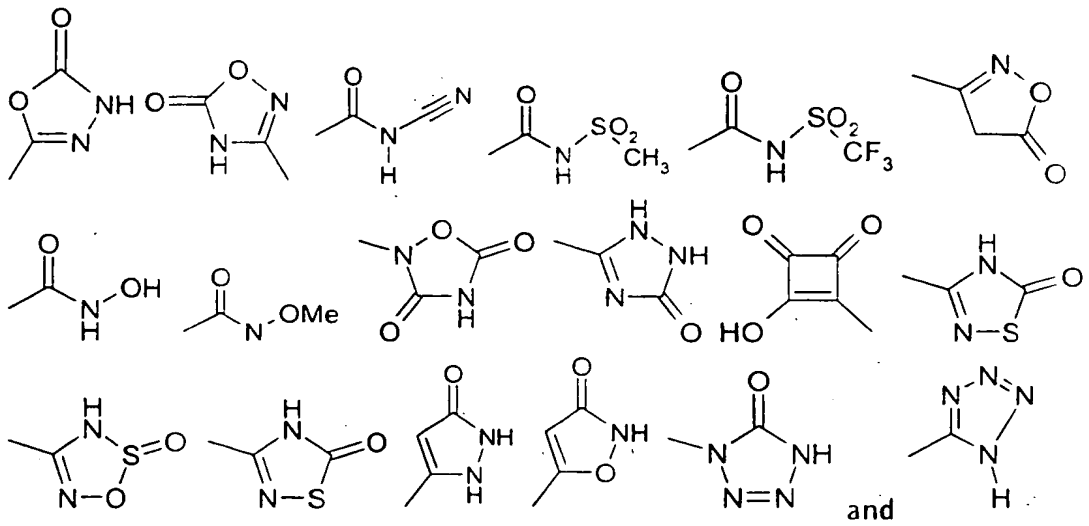
Va

wherein R^{10} is defined as above,

23) -NR^{10}-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one, two or three times by R13,

24) –O-CF_3 , or

25) a residue from the following list



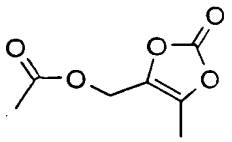
and

26) -(C_0-C_4)-alkylene-(C_6-C_{14})-aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R13 and is as defined above,

27) -(C_0-C_4)-alkylene-(C_4-C_{15})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

28) –(C_0-C_2)alkylene-C(O)-O-(C_1-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

29) –(C_0-C_2)alkylene-C(O)-O-(C_1-C_4)-alkylene-O-C(O)-O-(C_1-C_7)-alkyl,



30)

31) -(C_0-C_4)-alkylene-(C_3-C_8)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

32) -(C_0-C_4)-alkylene-het, wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

2. A compound of the formula I as claimed in claim 1, wherein

R^0 is 1. a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8,

2. a monocyclic or bicyclic 4- to 15-membered heteroaryl out of the group pyridyl, pyrimidinyl, indolyl, isoindolyl, indazolyl, phthalazinyl, quinolyl, isoquinolyl, benzothiophen, quinazolinyl and phenylpyridyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, or

3. a monocyclic or bicyclic 4- to 15-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, and which is additionally substituted by a monocyclic or bicyclic 4- to 15-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

R8 is 1. halogen,

2. $-NO_2$,

3. -CN,

4. $-C(O)-NH_2$,

5. -OH,

6. $-NH_2$,

7. $-O-CF_3$

8. a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by halogen or $-O-(C_1-C_8)$-alkyl,

9. $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,

10. $-O-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,

11. $-SO_2-CH_3$, or

12. $-SO_2-CF_3$

provided that R8 is at least one halogen, $-C(O)-NH_2$ or $-O-(C_1-C_8)$-alkyl residue, if R^0 is a monocyclic or bicyclic 6- to 14-membered aryl,

Q is a direct bond, $-(C_0-C_2)$-alkylene-$C(O)-NR^{10}$-, $-NR^{10}-C(O)-NR^{10}$-, $-NR^{10}-C(O)$-, $-SO_2$- or $-(C_1-C_6)$-alkylene,

R^1 is a hydrogen atom, -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R^{13}, -(C_1-C_3)-alkylene-C(O)-NH-R^0, -(C_1-C_3)-alkylene-C(O)-O-R^{15}, -(C_1-C_3)-perfluoroalkylene, -(C_1-C_3)-alkylene-S(O)-(C_1-C_4)-alkyl, -(C_1-C_3)-alkylene-$S(O)_2$-(C_1-C_3)-alkyl, -(C_1-C_3)-alkylene-$S(O)_2$-$N(R^{4'})$-$R^{5'}$, -(C_1-C_3)-alkylene-O-(C_1-C_4)-alkyl, -(C_0-C3)-alkylene-(C_3-C_8)-cycloalkyl, or -(C_0-C_3)-alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, whereas R^{14} is defined below,

$R^{4'}$ and $R^{5'}$ are independent of one another are identical or different and are hydrogen atom or -(C_1-C_4)-alkyl,

R^2 is a direct bond or –(C_1-C_4)-alkylene, or

R^1 and R^3 together with the atoms to which they are bonded form a 4- to 7-membered cyclic group, containing up to 1 or 2 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

R^1-N-R^2-V form a 4- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

R^{14} is halogen, -OH, =O, -(C_1-C_8)-alkyl, -(C_1-C_4)-alkoxy, -C(O)-OH, -CN, $-NH_2$, -C(O)-O-(C_1-C_4)-alkyl, -(C_1-C_8)-alkylsulfonyl, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-N-[(C_1-C_8)-alkyl]$_2$, -NR^{18}-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH_2, –NR^{18}-C(O)-NH-[(C_1-C_8)-alkyl]$_2$, wherein R^{18} is hydrogen atom, -(C_1-C_3)-perfluoroalkyl or –(C_1-C_6)-alkyl,

V is 1. a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

2. a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or

3. a monocyclic or bicyclic 4- to 15-membered heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

G is a direct bond, $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-C(O)-(CH_2)_n-$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n-$ or $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$,

n and m are are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

R^{10} is hydrogen atom, $-(C_1-C_3)$-perfluoroalkyl or $-(C_1-C_6)$-alkyl,

M is
1. a hydrogen atom,
2. $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
3. $-C(O)-NR^{11}R^{12}$,
4. $-(CH_2)_m-NR^{10}$,
5. $-(C_6-C_{14})$-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
6. $-(C_4-C_{15})$-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
7. (C_3-C_7)-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
8. a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, wherein R^{14} is defined above,

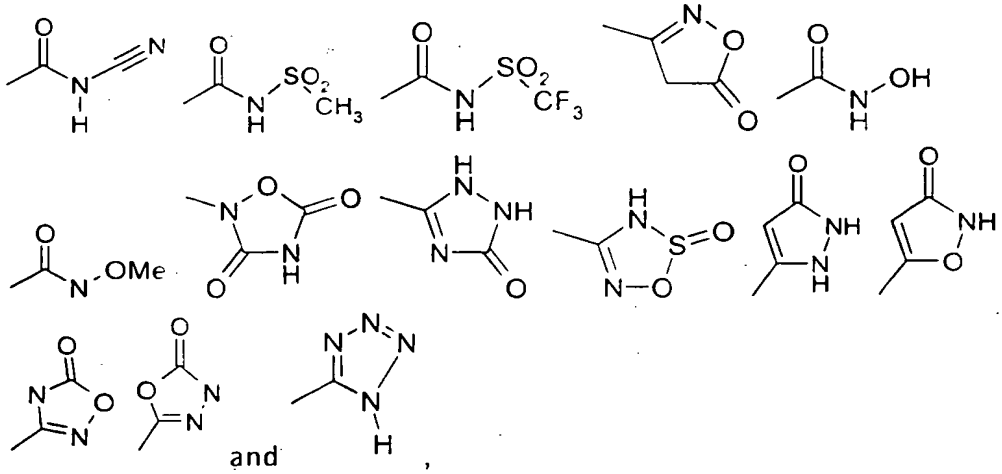
R^{11} and R^{12} are independently of one another identical or different and are
1. hydrogen atom,
2. $-(C_1-C_6)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

3. -(C_6-C_{14})-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} or

5. -(C_4-C_{15})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

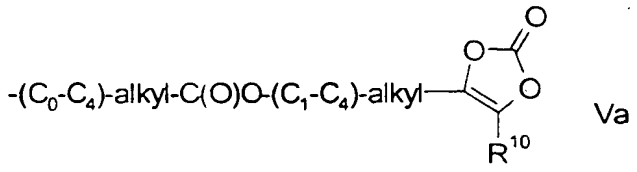
R^{11} and R^{12} together with the nitrogen atom to which they are bonded can form a saturated 4- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

R^{13} is halogen, -NO_2, -CN, =O, -OH, -(C_1-C_8)-alkyl, -(C_1-C_8)-alkoxy, -CF_3, phenyl, phenyloxy-, -C(O)-O-R^{11}, phenyl-(C_1-C_4)-alkoxy-, -C(O)-N-$R^{11}R^{12}$, -$NR^{11}R^{12}$, -NR^{10}-SO_2-R^{10}, -S-R^{10}, -SO_n-R^{10}, wherein n is 1 or 2; -SO_2-$NR^{11}R^{12}$, -C(O)-R^{10}, -(C_0-C_4)-alkyl-C(O)-O-C(R^{15}, R^{16})-O-C(O)-R^{17}, -(C_1-C_4)-perfluoroalkyl, -CN, -O-R^{15}, -(C_0-C_4)-alkylene-C(O)-O-C(R^{15}, R^{16})-O-C(O)-O-R^{17}, -O-CF_3,-C(O)-O-R^{15}, -C(O)-H, -NH-C(O)-NH-R^{10}, -NH-C(O)-O-R^{15}, -S(O)-(C_1-C_6)-alkyl, -$S(O)_2$-(C_1-C_6)-alkyl, -$S(O)_2$- $N(R^{10})$-R^{11}, -(C_1-C_3)-alkylene-O-(C_1-C_3)-alkyl or a residue from the following list



and ,

or a residue of formula Va,



Va

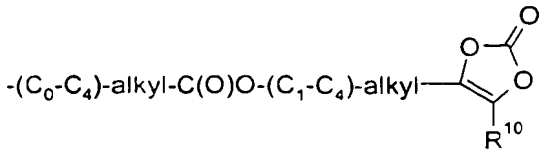
wherein R^{10}, R^{11},R^{12} are as defined above and R^{15}, R^{16} or R^{17} are as defined below,

R^{15} and R^{16} are independently of one another hydrogen, -(C_1-C_6)-alkyl, or together with the carbon atom to which they are bonded they form -(C_3-C_6)-cycloalkyl ring, which is unsubstituted or substituted one to three times by R^{10},

R^{17} is -(C_1-C_6)-alkyl, -(C_3-C_7)-cycloalkyl, -(C_1-C_6)-alkyl-(C_3-C_7)-cycloalkyl wherein said cycloalkyl ring is unsubstituted or substituted one to three times by R^{10}, and

R^3 and R^4 are identical or different and independent of one another are

1) hydrogen atom,
2) halogen,
3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R^{13},
4) -(C_1-C_3)-perfluoroalkyl,
5) phenyl, wherein phenyl is unsubstituted or substituted one to three times by R^{13},
6) -O-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R^{13},
7) -CN,
8) -OH,
9) phenyloxy-, wherein phenyloxy is unsubstituted or substituted one to three times by R^{13},
10) benzyloxy-, wherein benzyloxy is unsubstituted or substituted one to three times by R^{13},
11) -C(O)-O-R^{11},
12) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{12} ,
13) -N(R^{11})-R^{12},
14) -NR^{10}-SO_2-R^{10},
15) -SO_n-R^{10}, wherein n is 1 or 2,
16) -SO_2-N(R^{11})-R^{12},
17) -C(O)-O-C(R^{15}, R^{16})-O-C(O)-R^{17}, wherein R^{15}, R^{16} and R^{17} are as defined above,
18) -C(O)-O-C(R^{15}, R^{16})-O-C(O)-O-R^{17}, wherein R^{15}, R^{16} and R^{17} are as defined above,
19) residue of formula Va,



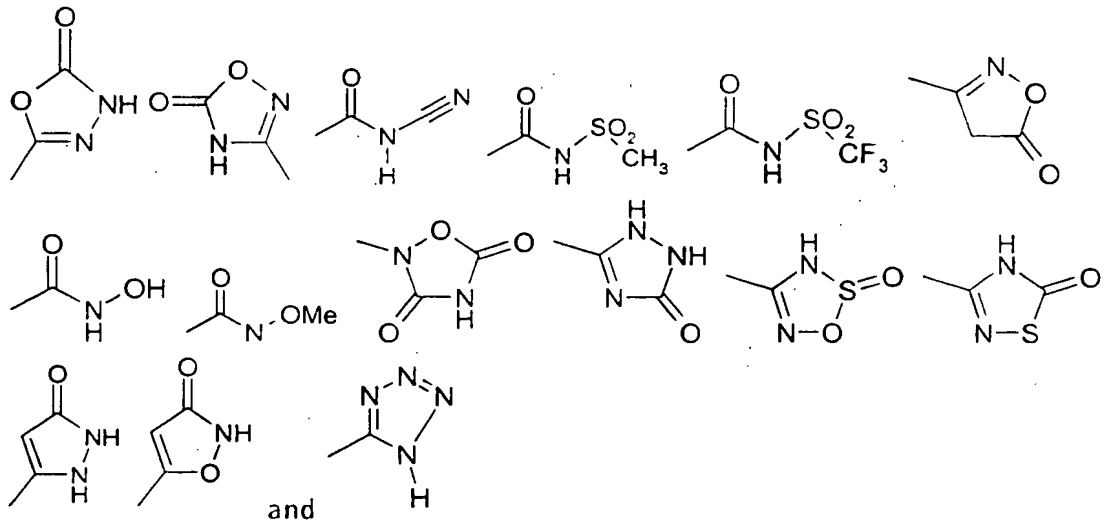
Va

wherein R^{10} is defined as above,

20) -NR^{10}-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R^{13},

21) –O-CF_3,

22) a residue from the following list



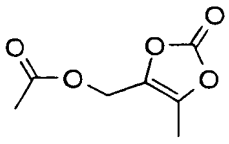
and

23) -(C_0-C_2)-alkylene-aryl, wherein aryl is a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R^{13}, wherein R^{13} is as defined above,

24) -(C_0-C_2)-alkylene-heteroaryl, wherein heteroaryl is a monocyclic or bicyclic 4- to 15-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

25) –(C_0-C_2)-alkylene-C(O)-O-(C_1-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

26) –(C_0-C_2)-alkylene-C(O)-O-(C_1-C_4)-alkylene-O-C(O)-O-(C_1-C_7)-alkyl,



27) ,

28) -(C_0-C_4)-alkylene-(C_3-C_8)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

29) -(C_0-C_4)-alkylene-het, wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{15}, R^{16} and R^{17} are as defined above,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

3. A compound of the formula I as claimed in claim 1 or claim 2, wherein

R^0 is 1. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

2. a bicyclic 4- to 15-membered heteroaryl selected out of the group indolyl, isoindolyl, benzofuranyl, benzothiophenyl, 1,3-benzodioxolyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, chromanyl, isochromanyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, purinyl and pteridinyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, , triazolyl, isothiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, pyridazinyl and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R8

3. a monocyclic 4- to 15-membered heteroaryl out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl,

thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R8

R8 is 1. F, Cl, Br or J,

2. $-C(O)-NH_2$,

3. $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -OH or a methoxy residue, or

4. $-O-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen or a methoxy residue,

provided that R8 is at least one halogen, $-C(O)-NH_2$ or $-O-(C_1-C_8)$-alkyl residue, if R^0 is a monocyclic or bicyclic 6- to 14-membered aryl,

Q is a direct bond, -C(O)-; $-SO_2-$, $-(C_1-C_6)$-alkylene, or $-(C_0-C_2)$-alkylene-$C(O)-NR^{10}-$,

R^1 is hydrogen atom, $-(C_1-C_2)$-alkyl, $-(C_1-C_3)$-alkylene-$C(O)-NH-R^0$, $-(C_1-C_3)$-alkylene-$C(O)-O-R^{15}$, $-(C_1-C_3)$-perfluoroalkyl, $-(C_1-C_3)$-alkylene-$S(O)_2-(C_1-C_3)$-alkyl or $-(C_1-C_3)$-alkylene-$S(O)_2-N(R^{4'})-R^{5'}$,

$R^{4'}$ and $R^{5'}$ are independent of one another are identical or different and are hydrogen atom or $-(C_1-C_2)$-alkyl,

R^2 is a direct bond or $-(C_1-C_2)$-alkylene, or

R^1-N-R^2-V form a 4- to 7- membered cyclic group out of the group azetidine, azetidinone, piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

R^{14} is halogen, -OH, =O, $-(C_1-C_8)$-alkyl, -C(O)-OH, -CN, $-NH_2$, $-C(O)-O-(C_1-C_4)$-alkyl, $-(C_1-C_8)$-alkylsulfonyl, $-C(O)-NH-(C_1-C_8)$-alkyl, $-C(O)-N-[(C_1-C_8)\text{-alkyl}]_2$, $-C(O)-NH_2$ or $-NR^{18}$, wherein R^{18} is hydrogen atom, $-(C_1-C_3)$-perfluoroalkyl or $-(C_1-C_6)$-alkyl,

V is 1. a 3- to 7-membered cyclic residue out of the group containing compounds which are derived from aziridine, azirine, azetidine, azetidinone, pyrrole, pyrrolidine, pyridonyl, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, tetrazine, tetrazole, azepine, diazirine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, pyridazine, piperidine, piperazine, pyrrolidinone, ketopiperazine, furan, pyran, dioxole, oxazole, isoxazole, 2-isoxazoline, isoxazolidine, morpholine, oxirane, oxaziridine, 1,3-dioxolene, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxaziridine, thiophene, thiopyran, thietan, thiazole, isothiazole, isothiazoline, isothiazolidine, 1,2-oxathiolan, thiopyran, 1,2-thiazine, 1,3-thiazole, 1,3-thiazine, 1,4-thiazine, thiadiazine or thiomorpholine, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

2. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or

3. a bicyclic 5- to 14-membered heteroaryl out of the group quinolyl, isoquinolyl and quinoxalinyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

G is a direct bond, $-(CH_2)_m-$, or $-(CH_2)_m-NR^{10}-$,

m is the integers zero, 1, 2, 3 or 4,

R^{10} is hydrogen atom, $-(C_1-C_3)$-perfluoroalkyl or $-(C_1-C_4)$-alkyl,

M is 1. a hydrogen atom,

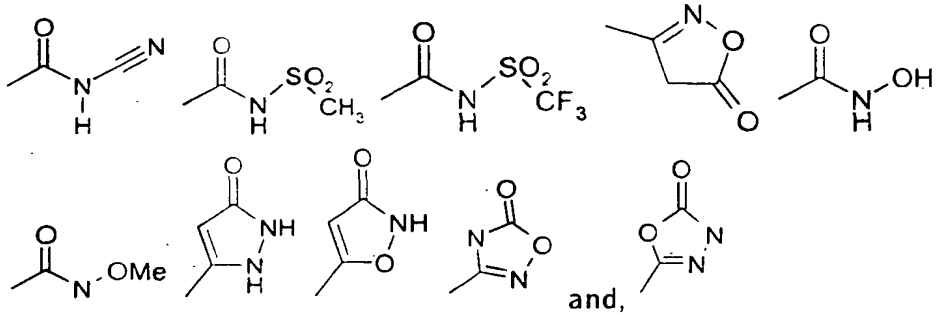
2. $-(C_4-C_{15})$-heteroaryl, wherein heteroaryl is a residue out of the group which can be derived from piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, pyridonyl, imidazole, pyridazine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, tetrahydropyran, thiadiazole or thiomorpholine, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

3. $-(C_1-C_6)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or

4. $-(C_3-C_6)$-cycloalkyl,

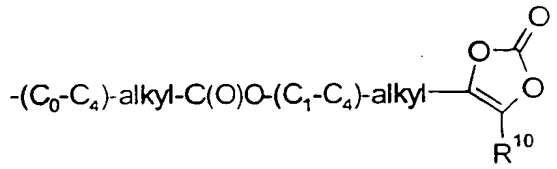
R^{11} and R^{12} together with the nitrogen atom to which they are bonded can form a saturated 4- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

R^{13} is halogen, $-NO_2$, -CN, =O, -OH, $-(C_1-C_8)$-alkyl, $-(C_1-C_8)$-alkoxy, $-CF_3$, $-C(O)-O-R^{11}$, $-C(O)-N(R^{11})-R^{12}$, $-N(R^{11})-R^{12}$, $-NR^{10}-SO_2-R^{10}$, $-SO_n-R^{10}$, wherein n is 1 or 2; $-SO_2-N(R^{11})-R^{12}$, $-C(O)-R^{10}$, $-(C_0-C_4)$-alkylene-$C(O)-O-C(R^{15}, R^{16})-O-C(O)-R^{17}$, $-(C_0-C_4)$-alkylene-$C(O)-O-C(R^{15}, R^{16})-O-C(O)-O-R^{17}$, $-(C_1-C_4)$-perfluoroalkyl, -CN, $-O-R^{15}$, $-O-CF_3$, $-C(O)-O-R^{15}$, $-NH-C(O)-NH-R^{10}$, $-S(O)-(C_1-C_6)$-alkyl, $-S(O)_2-(C_1-C_6)$-alkyl, $-S(O)_2-N(R^{10})-R^{11}$, $-(C_1-C_3)$-alkylene-$O-(C_1-C_3)$-alkyl, or a residue from the following list



and,

or a residue of formula Va,



Va

wherein R^{10}, R^{11},R^{12} are as defined above and R^{15}, R^{16} or R^{17} are as defined below,

R^{15} and R^{16} are independently of one another hydrogen, $-(C_1-C_4)$-alkyl, or together with the carbon atom to which they are bonded they form $-(C_3-C_6)$-cycloalkyl ring, which is unsubstituted or substituted one to three times by R^{10},

R^{17} is $-(C_1-C_6)$-alkyl, $-(C_3-C_6)$-cycloalkyl, $-(C_1-C_6)$-alkyl-(C_3-C_6)-cycloalkyl wherein said cycloalkyl ring is unsubstituted or substituted one to three times by R^{10},

R^3 and R^4, are independent of one another are identical or different and are

1) hydrogen atom,
2) halogen,

3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R^{13},

4) -(C_1-C_3)-perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or substituted one to three times by R^{13},

6) -O-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R^{13},

7) -CN,

8) -OH,

9) phenyloxy-, wherein phenyloxy is unsubstituted or substituted one to three times by R^{13},

10) benzyloxy-, wherein benzyloxy is unsubstituted or substituted one, two or three times by R^{13},

11) -C(O)-O-R^{11},

12) -(C_0-C_4)alkyl-C(O)-N(R^{11})-R^{12},

13) -N(R^{11})-R^{12},

14) -NR^{10}-SO_2-R^{10},

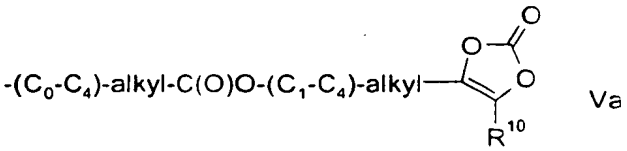
15) -SO_n-R^{10}, wherein n is 1 or 2,

16) -SO_2-N(R^{11})-R^{12},

17) -C(O)-O-C(R^{15}, R^{16})-O-C(O)-R^{17}, wherein R^{15}, R^{16} and R^{17} are as defined above,

18) -C(O)-O-C(R^{15}, R^{16})-O-C(O)-O-R^{17}, wherein R^{15}, R^{16} and R^{17} are as defined above,

19) a residue of formula Va,



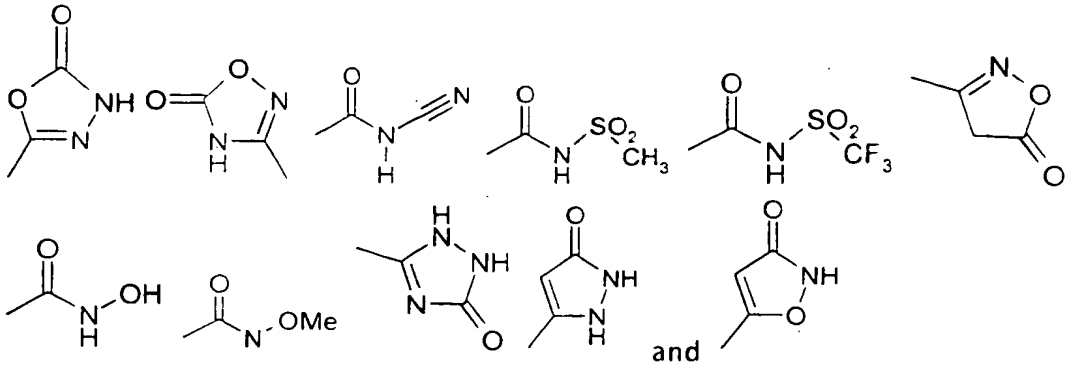
Va

wherein R^{10} is defined as above,

20) -NR^{10}-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R^{13},

21) –O-CF_3, or

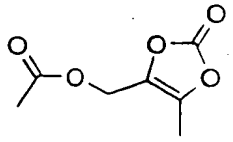
22) a residue from the following list



and

23) –(C_0-C_2)-alkylene-C(O)-O-(C_1-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

24) –(C_0-C_2)-alkylene-C(O)-O-(C_1-C_4)-alkylene-O-C(O)-O-(C_1-C_7)-alkyl, or

25) 

wherein R^{10}, R^{11},R^{12},R^{15}, R^{16} or R^{17} are as defined above,
in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

4. A compound of the formula I as claimed in one or more of claims 1 to 3, wherein

R^0 is 1. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

2. a bicyclic 5- to 14-membered heteroaryl selected out of the group indolyl, isoindolyl, benzofuranyl, benzothiophenyl, 1,3-benzodioxolyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, chromanyl, isochromanyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, purinyl and pteridinyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, , triazolyl, isothiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, pyridazinyl

and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8

3. a monocyclic 4- to 15-membered heteroaryl out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

R8 is 1. F, Cl, Br or J,

2. $-C(O)-NH_2$,

3. $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -OH or a methoxy residue, or

4. $-O-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen or a methoxy residue,

provided that R8 is at least one halogen, $-C(O)-NH_2$ or $-O-(C_1-C_8)$-alkyl residue, if R^0 is a monocyclic or bicyclic 6- to 14-membered aryl,

Q is a direct bond, -C(O)-; $-SO_2-$ or $-(C_1-C_6)$-alkylene or $-(C_0-C_2)$-alkylen-$C(O)-NR^{10}$-,

R^1 is hydrogen atom or $-(C_1-C_2)$-alkyl,

R^2 is a direct bond or $-(C_1-C_2)$-alkylene, or

R^1-N-R^2-V form a 5- to 7- membered cyclic group out of the group piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

R^{14} is halogen, -(C_1-C_4)-alkyl or -NH_2,

R^{11} and R^{12} together with the nitrogen atom to which they are bonded can form a saturated 4- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

V is 1. a 3- to 7-membered cyclic residue out of the group containing compounds which are derived from
aziridine, azirine, azetidine, pyrrole, pyrrolidine, pyridonyl, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, tetrazine, tetrazole, azepine, diazirine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, pyridazine, piperidine, piperazine, pyrrolidinone, ketopiperazine, furan, pyran, dioxole, oxazole, isoxazole, 2-isoxazoline, isoxazolidine, morpholine, oxirane, oxaziridine, 1,3-dioxolene, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxaziridine, thiophene, thiopyran, thietan, thiazole, isothiazole, isothiazoline, isothiazolidine, 1,2-oxathiolan, thiopyran, 1,2-thiazine, 1,3-thiazole, 1,3-thiazine, 1,4-thiazine, thiadiazine or thiomorpholine, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
2. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
3. a bicyclic 5- to 14-membered heteroaryl out of the group quinolyl, isoquinolyl and quinoxalinyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

G is a direct bond, -$(CH_2)_m$-, or -$(CH_2)_m$-NR^{10}-,
m is the integers zero, 1, 2, 3 or 4,
R^{10} is hydrogen atom, -(C_1-C_3)-perfluoroalkyl or -(C_1-C_4)-alkyl,

M is 1. a hydrogen atom,
2. -(C_4-C_{15})-heteroaryl, wherein heteroaryl is a residue out of the group which can be derived from piperidine, piperazine, pyridine, pyrimidine, pyrrolidine,

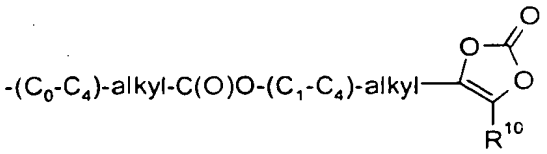
pyrrolidinone, pyridonyl, imidazole, pyridazine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, tetrahydropyran, thiadiazole or thiomorpholine, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

3. -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or

4. (C_3-C_6)-cycloalkyl,

$R^3$and R^4 are independent of one another are identical or different and are

1) hydrogen atom,
2) halogen,
3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R^{13},
4) -(C_1-C_3)-perfluoroalkyl,
5) phenyl, wherein phenyl is unsubstituted or substituted one to three times by R^{13},
6) -O-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R^{13},
7) -CN,
8) -OH,
9) -C(O)-O-R^{11},
10) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{12} ,
11) -N(R^{11})-R^{12},
12) -NR^{10}-SO_2-R^{10},
13) -SO_n-R^{10}, wherein n is 1 or 2,
14) -SO_2-N(R^{11})-R^{12},
15) -C(O)-O-C(R^{15}, R^{16})-O-C(O)-R^{17}, wherein R^{15}, R^{16} and R^{17} are as defined above,
16) -C(O)-O-C(R^{15}, R^{16})-O-C(O)-O-R^{17}, wherein R^{15}, R^{16} and R^{17} are as defined above,
17) a residue of formula Va,



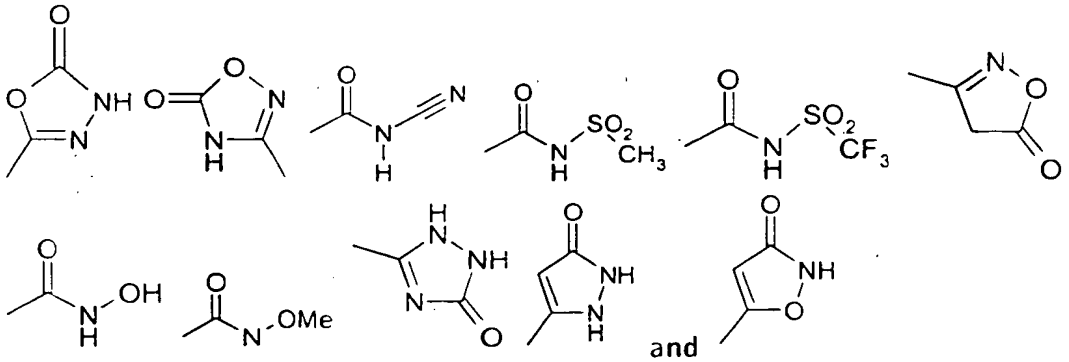
Va

wherein R^{10} is defined as above,

18) $-NR^{10}-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R^{13},

19) $-O-CF_3$,

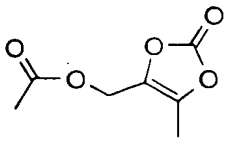
20) a residue from the following list



and

21) $-(C_0-C_2)$-alkylene-C(O)-O-(C_1-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

22) $-(C_0-C_2)$-alkylene-C(O)-O-(C_1-C_4)-alkylene-O-C(O)-O-(C_1-C_7)-alkyl, or

23) 

wherein R^{10}, R^{11},R^{12},R^{15}, R^{16} or R^{17} are as defined above,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

5. A compound of the formula I as claimed in one or more of claims 1 to 4, wherein

R^0 is 1. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R8,

2. a monocyclic 4- to 14-membered heteroaryl out of the group thienyl, thiadiazolyl, isoxazolyl and thiazolyl, wherein said heteroaryl is substituted by a residue selected out of the group thienyl, 2-thienyl and 3-thienyl, wherein said

residue is unsubstituted or mono- or disubstituted independently of one another by R8,

R^8 is F, Cl, Br, $-OCH_3$, $-C(O)-NH_2$ or $-O-CF_3$,

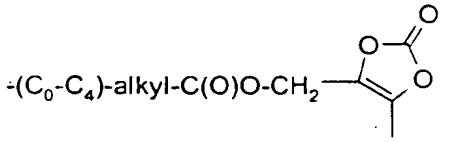
Q is a direct bond, -C(O)-; $-SO_2-$, methylene or ethylene,

R^1 is hydrogen atom,

R^2 is a direct bond or methylene, or

R^1-N-R^2-V form a 4- to 7-membered cyclic group out of the group azetidine, pyrrolidine, piperidine and piperazine,

R^{13} is -OH, =O, -F, $-CF_3$, $-C(O)-O-R^{11}$, $-C(O)-N(R^{11})-R^{12}$, $-N(R^{11})-R^{12}$, $-NR^{10}-SO_2-R^{10}$, $-SO_n-R^{10}$, wherein n is 1, 2 or 3; (C_1-C_6)-alkyl, (C_0-C_3)-alkylene-O-(C_0-C_4)-alkyl, $-SO_2-N(R^{11})-R^{12}$, $-C(O)-R^{10}$, $-(C_0-C_4)$-alkylene-$C(O)-O-C(R^{15}, R^{16})-O-C(O)-R^{17}$, $-(C_0-C_4)$-alkyl-$C(O)-O-C(R^{15}, R^{16})-O-C(O)-O-R^{17}$, or a residue of formula Va,



Va

wherein R^{10}, R^{11},R^{12},R^{15}, R^{16} or R^{17} are as defined above,

R^{14} is halogen, methyl, ethyl or $-NH_2$,

V is 1. a residue out of the group containing compounds which is derived from isoquinoline, quinoline, quinazoline, piperidine, azetidine, pyrrolidine, tetrahydropyrane, piperazine and isoxazole,
wherein said cyclic residue is unsubstituted or mono- or disubstituted independently of one another by R^{14}, or

2. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R^{14}, or

G is a direct bond, $-(CH_2)_m-$, or $-(CH_2)_m-NR^{10}-$,

m is the integers zero, 1 or 2,

R^{10} is hydrogen atom or $-(C_1-C_4)$-alkyl,

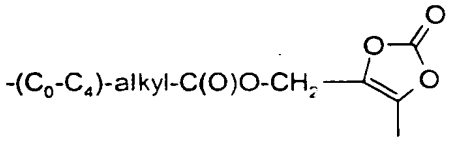
M is a hydrogen atom, (C_2-C_4)-alkyl, imidazolyl, pyrazolyl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, pyridinyl, pyrimidyl, pyrazinyl, pyridazinyl, or $-(C_3-C_6)$-cycloalkyl, wherein said cyclic residues are unsubstituted or mono- or disubstituted independently of one another by R^{14}

R^{11} and R^{12} together with the nitrogen atom to which they are bonded can form a saturated 4- to 7-membered monocyclic heterocyclic ring which in addition to the

nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen out of the group azetidine, pyrrolidine, morpholine, thiomorpholine, piperazine, piperidine; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

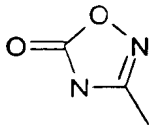
$R^3$and R^4 are independent of one another are identical or different and are

1. hydrogen atom,
2. F or Cl,
3. -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted by R^{13},
4. phenyl, wherein phenyl is unsubstituted or substituted one to three times by R^{13},
5. -O-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted by R^{13},
6. -C(O)-O-R^{11},
7. -(C_0-C_2)-alkyl-C(O)-N(R^{11})-R^{12} ,
8. -N(R^{11})-R^{12} ,
9. -NR^{10}-SO_2-R^{10},
10. -SO_2-N(R^{11})-R^{12} ,
11. -C(O)-R^{10},
12. -C(O)-O-C($R^{15}R^{16}$)-O-C(O)-R^{17}, wherein R^{15}, R^{16} and R^{17} are as defined above,
13. -C(O)-O-C($R^{15}R^{16}$)-O-C(O)O-R^{17}, wherein R^{15}, R^{16} and R^{17} are as defined above,
14. a residue of formula Va

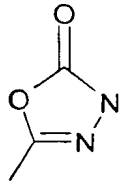


Va

15. a residue of formula Vb or Vc,

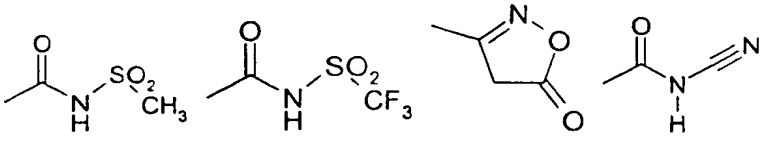


Vb



Vc

16. a residue from the following list



17. –CN or
18. -CF_3

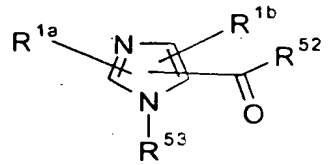
in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

6. A compound of the formula I as claimed in one or more of claims 1 to 5, wherein the compound of the formula I is
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
5-Chloro-3-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-phenyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-ethyl-5-methyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-ethyl-5-methyl-1H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-iodo-5-methyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-iodo-5-methyl-1H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-1H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-cyclopropyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(2,6-difluoro-phenyl)-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-cyclopentyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(2-methoxy-ethyl)-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(2,6-dichloro-phenyl)-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-isopropyl-3H-imidazole-4- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-pyridin-2-yl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-2-phenyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-2-phenyl-1H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-pyridin-3-yl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(2-methyl-thiazol-4-yl)-3H- imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(2-methyl-thiazol-4-yl)-1H- imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-ethanesulfonyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-3H-imidazole-2,4-dicarboxylic acid 2-amide 4-[(1-isopropyl-piperidin-4-yl)-amide],
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-1H-imidazole-2,4-dicarboxylic acid 2-amide 4-[(1-isopropyl-piperidin-4-yl)-amide],
2-Bromo-3-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
2-Bromo-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-1H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
2-(4-Chloro-phenyl)-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-[(4-Chloro-phenylcarbamoyl)-methyl]-2-methoxymethyl-3H-imidazole-4-carboxylic acid (1- isopropyl-piperidin-4-yl)-amide,
1-[(4-Chloro-phenylcarbamoyl)-methyl]-2-methoxymethyl-1H-imidazole-4-carboxylic acid (1- isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-ethanesulfonyl-1H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

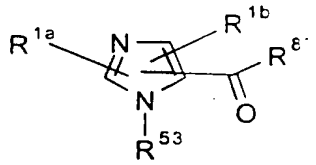
5-Chloro-3-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]-2-phenyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-cyclopropyl-1H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(2-methoxy-phenyl)-5-methyl-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide or
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(3-trifluoromethyl-phenyl)-3H-imidazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide.

7. A process for the preparation of a compound of the formula I as claimed in one or more of claims 1 to 6, which comprises condensing a compound of the formula **29** with a compound of the formula $HR^{8'}$ to give a compound of the formula **30** and optionally converting the compound of the formula **30** into a compound of the formula I,



$HR^{8'}$ ⟶

29



⟶ formula I

30

wherein the residue $R^{8'}$ has the donation of $-N(R^1)-R^2-V-G-M$ as indicated in claims 1 to 6, but where in $R^{8'}$ functional groups can also be present in the form of groups that are subsequently transformed into the final functional groups present in $-N(R^1)-R^2-V-G-M$, and where the residue R^{53} denotes the group $-Q-R^o$ or can denote a group which is subsequently transformed into the group $-Q-R^o$, and where the group $-C(O)-R^{52}$ can be a carboxylic acid group or derivatives thereof, and where the groups R^{1a} and R^{1b} in the formulae **29** and **30** have the corresponding definitions of R^3 and R^4 in formula I as defined in claims 1 to 6 or functional groups in them can also be present in protected form or in the form of precursor groups.

8. A pharmaceutical preparation, comprising at least one compound of the formula I as claimed in one or more of claims 1 to 6 in all its stereoisomeric forms and mixtures thereof in any ratio and/or its physiologically tolerable salts and a pharmaceutically acceptable carrier.

9. The use of a compound of the formula I as claimed in one or more of claims 1 to 6 in all its stereoisomeric forms and mixtures thereof in any ratio and/or their physiologically tolerable salts for the production of pharmaceuticals for inhibition of factor Xa and/or factor VIIa or for influencing blood coagulation or fibrinolysis.

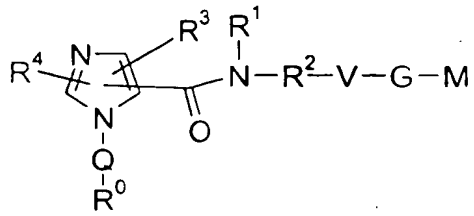
10. The use as claimed in claim 9 for influencing blood coagulation, inflammatory response, fibrinolysis, cardiovascular disorders, thromboembolic diseases, restenoses, abnormal thrombus formation, acute myocardial infarction, unstable angina, acute vessel closure associated with thrombolytic therapy, thromboembolism, percutaneous, pathologic thrombus formation occurring in the veins of the lower extremities following abdominal, knee and hip surgery, transluminal coronary angioplasty, transient ischemic attacks, stroke, disseminated systemic intravascular coagulatopathy occurring in vascular systems during septic shock, a risk of pulmonary thromboembolism, certain viral infections or cancer, intravascular coagulatopathy occurring in vascular systems during septic shock, coronary heart disease, myocardial infarction, angina pectoris, vascular restenosis, for example restenosis following angioplasty like PTCA, adult respiratory distress syndrome, multi-organ failure, stroke and disseminated intravascular clotting disorder, thromboses like deep vein and proximal vein thrombosis which can occur following surgery.

Abstract

DEAV2002/0085

Imidazole-derivatives as factor Xa inhibitors

The present invention relates to compounds of the formula I,



(I)

wherein R^0 ; R^1 ; R^2 ; R^3 ; R^4; Q; V, G and M have the meanings indicated in the claims. The compounds of the formula I are valuable pharmacologically active compounds. They exhibit a strong antithrombotic effect and are suitable, for example, for the therapy and prophylaxis of cardiovascular disorders like thromboembolic diseases or restenoses. They are reversible inhibitors of the blood clotting enzymes factor Xa (FXa) and/or factor VIIa (FVIIa), and can in general be applied in conditions in which an undesired activity of factor Xa and/or factor VIIa is present or for the cure or prevention of which an inhibition of factor Xa and/or factor VIIa is intended. The invention furthermore relates to processes for the preparation of compounds of the formula I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical preparations comprising them.